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MEETING ABSTRACTS Open Access

Lupus 2014: New Targets, New Approaches

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MEETING ABSTRACTS

A1

Moving lupus epidemiology forward: returning to the basics

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The protracted diagnostic period and variable disease presentation not only complicate diagnosing SLE but also the epidemiologic study of it. Coupled with the remitting and relapsing nature of the disease and the challenges in managing it, clinical research in lupus requires careful attention to study design, control selection, temporality, and many often overlooked issues in the analysis phase. Between "big data" and the impressive advances in the basic sciences, it is tempting to either oversimplify methods to take advantage of "big data" or overcomplicate because the problem itself is complicated.

As we revisit the building blocks of epidemiologic research, we will uncover opportunities to move epidemiology and clinical research forward in SLE. Why do we care about effect modification and what is it? Why can we not just adjust for everything that we want to? And perhaps, most importantly, going back to the very beginning and asking ourselves: does this matter?

During this talk we will discuss issues relating to case identification methods, potential biases associated with control selection, and return to the basics of epidemiologic research. Although we shall discuss these issues in the context of environmental (nongenetic) factors, these concerns extend across the worlds of observational data analysis, can impact randomized trials, and are relevant for all types of exposures and outcomes.

A2

Is prevention of systemic lupus erythematosus a goal?

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Background: Prevention of systemic lupus erythematosus (SLE) presents many challenges. By contrast, prevention of acquired immunodeficiency syndrome (AIDS) is relatively straightforward: an infective agent has been identified, risk behaviors are well-delineated, antiviral therapeutics are highly effective and neonates have been apparently cured. Lupus is a more complex disease, with a significant but incompletely defined genetic component, widely heterogeneous manifestations and major gaps in knowledge about pathogenesis.

Methods: The characteristic features of SLE can be exploited in the quest for preventive strategies. One of these is the presence of a latent phase during which expressed autoantibodies are increasing in number and complexity prior to the onset of clinical symptoms. This offers a path to the development of screening blood tests that would be cost-effective and generally acceptable to subjects. ANA alone is clearly not sufficient to establish risk, as it is highly prevalent in the healthy population. Alternatively, a panel of autoantibodies, possibly combined with cytokines and gene expression levels, might be useful. The skewed demographics of SLE can also be exploited, including the higher prevalence in females, first-degree relatives and individuals < 40 years old, permitting focus on those who are most likely to be at risk.

Results: A composite index, with demographics and multiplex blood autoantibody profiles, has been proposed. This index showed statistically significant correlation with progression of disease in a small prospective cohort ($P = 1 \times 10^{-7}$). As the science improves, the risk definition could be augmented with targeted genetic information, as is now available for several inherited cancers; even the simple inclusion of family history as a proxy for genetic input might be of value. All such screening efforts would be for naught in the absence of an available intervention. Fortunately, several candidate treatments are available for the incomplete lupus phenotypes, and precedent for using therapeutics in individuals who are not yet ill has been established in other conditions, notably type I diabetes mellitus.

Conclusions: It is timely to propose a prevention trial in individuals at high risk for development of SLE. A placebo arm would probably be required in such a study to show that the enrollment criteria successfully identified high-risk individuals. Challenges to trial design include acceptance of "no treatment" by persons profiled as high risk and the relatively long timeline likely to be required to achieve observable clinical change. However, despite these issues, available tools and therapeutics make prevention trials in SLE a feasible, near-term prospect.

A3

Are patient ratings of interactions with providers and health plans associated with technical quality of care in systemic lupus erythematosus?

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Background: Prior research has shown that the technical quality of SLE care is associated with the degree of subsequent accumulated damage. However, it is not known whether the nature of interactions between patients and providers and health systems is associated with the technical quality of care.

Methods: We analyzed data from the UCSF Lupus Outcomes Study (LOS), a national sample of persons with SLE interviewed annually using a structured telephone survey. The survey includes batteries from the Consumer Assessment of Health Plans developed by the US Agency for Healthcare Research and Quality and the Interpersonal Processes of Care

Table 1(abstract A3) Technical quality of care pass rates by ratings of healthcare experiences in SLE, aggregate

Number of dimensions	QI pass rate (95% CI)
None	0.71 (0.68, 0.74)
One to three	0.70 (0.67, 0.72)
Four to six	0.63 (0.58, 0.68)

Scales to rate care along six dimensions about providers (patient-provider communication, shared decision-making, and trust) and health systems (promptness/timeliness of care, care coordination, and assessment of health plans) from 0 to 100. Due to the fact that the ratings were not normally distributed, we dichotomized the measures at the lowest versus the highest three quartiles. The survey also includes the 13 quality indicators (QIs) for SLE that can be reliably reported by patients. The QIs were aggregated into a pass rate, defined as the number of QIs received as a proportion of those for which individuals are eligible. We used generalized estimating equations to model the relationship of the QI pass rate with being in the lowest quartile of ratings of each individual dimension and with being in the lowest quartile on zero, one to three, and four to six of the dimensions. Models were adjusted for age, race/ethnicity, education, poverty status, presence and kind of health insurance, specialty of principal SLE physician, disease duration, disease activity (SLAQ), and disease damage (BILD).

Results: A total of 640 LOS participants with ≥1 visit to their principal SLE provider in the year prior to interview were eligible for analysis. Mean age was 52.8 ± 12.6 years and mean disease duration was 20.1 ± 8.8 years; 38% were nonwhites, and 14% were in poverty. Being in the lowest quartile of ratings on any one individual dimension was not associated with a statistically significant difference in QI pass rates (data not shown). Being in the lowest quartile of ratings on four to six dimensions was associated with significantly lower pass rates (0.63 vs. 0.71 for those in the lowest quartile on no dimensions, $P = 0.02$) (Table 1).

Conclusions: Low ratings on multiple dimensions of interactions may be a sentinel for poor technical quality of care. In the USA, ratings of providers and health plans are in the public domain and this information can help persons with SLE choose providers and health plans more likely to achieve high technical quality of care.

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A4

Targeted delivery of PGE_2 ameliorates autoimmune nephritis

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Arthritis Research & Therapy 2014, **16(Suppl 1):**A4

Background: In SLE, pathogenic mechanisms responsible for immune activation, immune deposit formation, cell infiltration and organ damage are complex and variable. However, immune cells and their products contribute to the nature and intensity of organ involvement as well as the host's response to therapy. In many respects, renal involvement is a microcosm of systemic disease, with variable glomerulonephritis, interstitial nephritis and vasculitis. Both systemic autoimmune and renal cellular responses influence individual disease phenotype. Nevertheless, antigenic specificity determines local events, in particular where immune deposits form. Direct binding of autoantibodies to glomerular antigens is particularly relevant, and the site of complex formation, along with the capacity of deposited Ig to engage FcR and activate complement play important roles in disease expression. Cellular infiltration (for example, T cells, B cells, macrophages) and the renal cellular response to these events are also important and influential. For the most part, therapy is systemic and directed at controlling inflammation and autoimmunity, rationalizing that limiting autoreactivity and inflammatory cell infiltration will control disease. Although this approach is somewhat efficacious, it has limitations. Thus, we reasoned that in some circumstances, targeted therapy could provide advantage of better ongoing disease in a given organ, while sparing systemic side effects.

Methods: To approach this problem, we postulated that human monoclonal anti-α3(IV) antibodies (Ab) that localize in glomeruli could serve as vehicles for targeted drug delivery for glomerular diseases, including lupus nephritis. As a potential disease-modifying agent, we took advantage of recent observations that PGE_2 enhanced renal cellular recovery and regeneration after established immunologic injury during the course of nephrotoxic nephritis (NTN). To enhance efficacy and limit undesirable systemic effects and target the kidney, PGE_2 was coupled to a human monoclonal anti-α3(IV) Ab. Given enhanced glomerular expression of α3(IV), with very limited epitope exposure in other organs, it provides an ideal target for delivery of glomerular disease modifying agents. Therefore, PGE_2 was chemically linked to human anti-α3(IV) Ab. Chemical composition of conjugates was assessed by western blotting, and preserved anti-α3(IV) activity was confirmed by ELISA.

Results: Initially, glomerular localization of the anti-α3(IV) Ab-PGE_2 conjugates was determined after injection in normal mice (IF). Once confirmed, the capacity of the conjugates to modify disease was determined during established NTN. Proteinuria, BUN levels and histology normalized in PGE_2 conjugate-treated mice, as compared with untreated mice or mice treated with an equivalent dose of PGE_2 alone.

Conclusions: The results provide a novel means of targeting glomeruli during systemic disease, by providing efficient drug delivery, while limiting systemic effects.

A5

Lupus skin disease

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Arthritis Research & Therapy 2014, **16(Suppl 1):**A5

Skin findings in lupus erythematosus: The skin findings in lupus erythematosus include lupus-specific and lupus-nonspecific categorizations. Lupus specific includes chronic cutaneous, subacute cutaneous, and acute cutaneous lupus. Lupus-specific findings include having a skin biopsy that shows LE-specific histology. The diagnosis of cutaneous lupus can be made regardless of whether the patient meets ACR or SLICC criteria for lupus. Lupus-nonspecific skin findings refer to lesions such as vasculitis or urticaria, where the findings are not histopathologically distinct for lupus and/or may be seen as a feature of other disease processes beyond lupus erythematosus. Chronic cutaneous lupus includes localized, generalized, and hypertrophic lupus, lupus panniculitis, and papulomucinous lupus. There is currently an ongoing international Delphi approach to unify the classification of cutaneous lupus, since the ongoing proliferation of how best to group the various presentations of cutaneous lupus is confusing.

Skin and SLE criteria: Four of the SLE criteria are dermatologic, and the number of skin criteria contributes to there being many skin predominant lupus patients who meet criteria for SLE. Another approach to how best to classify SLE was recently published by the SLICC group. There is recognition of the variety of skin lesions that can be seen with the new criteria, but some criteria such as alopecia may be difficult in terms of attribution to lupus. The specificity of the new criteria will require ongoing investigation. In addition, some patients with cutaneous lupus initially do progress to SLE, but recent data suggest that, during progression to SLE, the SLE criteria are often met with skin, arthritis, hematologic, and serologic findings.

Pathophysiology and triggers of cutaneous lupus erythematosus: The pathophysiologic findings of cutaneous lupus include interface dermatitis, with dendritic cells, CD4 and CD8 lymphocytes, and activation of innate immune proteins, including antimicrobial peptides. An interferon signature is seen in the skin and frequently in the blood with patients with cutaneous lupus, and this correlates with the activity of lupus in the skin. There is evidence that medications are a frequent trigger of subacute cutaneous lupus, with about one-third of patients having drugs as a trigger or aggravating factor. In particular, medications such as terbinafine, TNF inhibitors, and omeprazole, in addition to usual culprits such as thiazide, should be considered as risk factors.

Quality of life and cutaneous lupus erythematosus: Recent studies indicate an extremely large impact of cutaneous lupus on quality of life,

particularly related to activity of the skin disease. Studies with the SF-36 demonstrate that domains related to mental health, role emotion, and social function are worse in cutaneous lupus than in type II diabetes and recent myocardia infarction. Sixty percent of cutaneous lupus patients are depressed.

Measurement of disease severity in cutaneous lupus erythematosus: The cutaneous lupus erythematosus area and severity index (CLASI) is a way to measure skin severity. The CLASI has undergone many validation studies for inter-rater and intra-rater reliability, responsiveness, correlation with QoL, and correlation with disease biomarkers. The CLASI has been studied in many different ethnic and racial groups, and has now been used in large international multicenter trials. These studies have demonstrated the importance of smoking as a risk factor for onset and severity in cutaneous lupus, as well as lack of responsiveness to current treatments.

Treatment of cutaneous lupus erythematosus: There is still a paucity of successful trials for cutaneous lupus. Hydroxychloroquine works for 50 to 60% of patients. Addition of quinacrine to hydroxychloroquine can improve response in two-thirds of patients refractory to hydroxychloroquine alone. There is a correlation of hydroxychloroquine levels with response. Lenalidomide appears to have been beneficial in two small open-label trials of refractory cutaneous lupus. Rituximab has helped some patients with refractory bullous lupus, a disease normally mediated by antibodies against type VII collagen. With the improved understanding of pathogenesis, measures of disease severity, and the understanding of the impact of lupus skin disease on patients, there is increasing interest in improving the approaches to treatment for patients.

A6

Modeling the stochastic behavior of lupus

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Background: Looking forward to preclinical risk assessment and early interventions: A major aspiration of clinical medicine is early diagnosis and interventions that interrupt autoimmune diseases in its earliest stages, before they become increasingly difficult and dangerous to treat. Definition of the relative contributions of three critical components at the earliest phases of disease is required to realize this goal: 1) genes; 2) environment; and 3) chance. Lupus, like all common human disorders, results from the interplay of these components. Currently >35 allelically variant genes, many of which are shared with other autoimmune disorders, are reported to contribute to the pathogenesis of lupus. The roadmap for genetic risk assessment is relatively straightforward. Even given that present studies are confounded by the failure of defined genetic variation to fully account for disease heritability, definition of the genetic components can be generated digitally through deep genome sequencing, genome wide association (GWA) studies and family linkage studies. However, thinking forward to the best-case scenario in which all heritability is explained, there will still be a substantial gap. This gap is commonly attributed to unknowns casually referred to as environmental factors and chance events. The importance of these extragenetic unknowns is underscored by studies of monozygotic twins, which have typically revealed >70% discordance for common autoimmune syndromes, including lupus. While epigenetic mechanisms may eventually explain some of this discordance, nebulously defined environmental factors and chance will continue to cloud genome-based risk prognostications and limit the potential for identifying individuals with sufficient genetic evidence to justify early interventions.

What are contributions of environment?: The identification of relevant environmental factors is in its infancy. Lupus flares caused by sunburn and drug-induced lupus-like syndromes stand out as well described environmental triggers, but the larger question of environmental exposure history, including prior viral infections, gut microbiome composition, chemical exposures, and what have you, that promote lupus pathogenesis will only be incrementally solved. Extracting the contributions of environmental factors would be made more tractable by first understanding the extent to which chance confounds the ability to derive cause-effect relationships between environment and disease.

What is the contribution of chance?: That which cannot be attributed to environmental factors would logically fall into the nebulous category of chance, termed more scientifically as stochastic behavior. This indeterminate parameter is increasingly recognized to be an integral component of all physical and biological systems. The prototype is Brownian motion of a particle traveling through a solution and colliding with molecules in a random manner. While random and unpredictable at the inception, stochastic behavior become biologically relevant if the "collision" initiates a chain of molecular and/or cellular processes that evolve into measurable "deterministic" behaviors. Thus, the chance engagement of molecule A with molecule B within a critical cell type cell or the chance cognate engagement of a critical cell type (such as a naïve $CD4^+$ T cell) with an antigen presenting cell (APC) could trigger the development of lupus.

The intrinsic variability of inbred strains of laboratory mice provides a means to understand the impact of stochastic behavior on disease: Investigation into the potential contributions of stochastic factors in complex disease processes is not practical in humans. Inbred strains of laboratory mice are the mammalian organism best suited for the task. Missing heritability as a confounding factor is negligible in highly inbred laboratory mice of the same inbred strain because each mouse is an identical twin. Environmental variation that cannot be readily controlled in humans can be minimized in mice by consistent husbandry in a stable laboratory colony.

The BXSB.*Yaa* model of lupus: BXSB male mice carrying the *Yaa* mutation spontaneously develop a systemic autoimmune disease with multiple similarities to severe forms of human lupus. A duplicated copy of Toll-like receptor 7 (*Tlr7*) caused by the *Yaa* mutation is the primary genetic cause of this lethal lupus-like disease. The consequence of the *Tlr7* duplication - realized only in *Yaa* males - is the potent evocation of the IFN1 response starting at a remarkably young age and the development of follicular T cells (T_{FH}) that secrete IL21 and drive massive germinal center B cell and plasmablast expansions. This results in high levels of autoantibodies to RNA, DNA and other self-antigens, formation of nucleic acid containing immune complexes and lethal immune complex-mediated glomerulonephritis that lead to premature deaths.

Methods and results: Robust variation in the autoimmune disease outcomes is apparent in individual BXSB.*Yaa* with uniform genetics and husbandry environment: BXSB.*Yaa* mice have been inbred for at least 100 generations, 50 of which were performed in our colony. At least to the depth of genetic analysis performed to date, our BXSB.*Yaa* colony is genetically fixed. Moreover, continuous microbial monitoring has not revealed any changes over the last 20 years. Thus as a first approximation the environment in our BXSB.*Yaa* research colony is notably stable.

However, we repeatedly observe substantial variation in the timing and severity of autoimmune disease among individual, highly inbred BXSB.*Yaa* mice in well-powered studies measuring overall mouse survival (example Figure 1A). This variation is not consistent with genetic drift and/or fitness selection for healthier breeders. Substantial disease variation determined here by outcomes (timing of survival) is a durable feature of inbred BXSB.*Yaa* mice.

Robust variation in longitudinal expression of T_{FH} in blood is observed in BXSB.*Yaa* mice at early stages of disease: Variation in the survival times of BXSB.*Yaa* would predict that biomarkers of mechanistically important cellular processes would vary similarly. Variation in such biomarkers at early stages of disease would be of most value because they may identify targets for early therapeutic interventions. T_{FH} are critical drivers of the BXSB.*Yaa* disease. Preliminary longitudinal studies investigating the expression of circulating $ICOS^+$ $CD4^+$ T cells show remarkable individual variation in the frequencies of these cells by at least 8 weeks of age (Figure 1B). While such results are not yet linked to the timing of survival of the mice or correlated with other important biomarkers of disease, it is reasonable to surmise that stochastic events acting within weeks of birth bifurcate into important deterministic processes (activation and expansions of T_{FH} in this case) that may be have long term consequences.

Conclusions: Much can be learned by embracing the concept of stochastic behavior: The principles described here are unlikely to be restricted to BXSB.*Yaa* mice. Virtually all genetically homogenous models of disease demonstrate a range of variation in disease timing and severity. It is therefore likely that stochastic principles broadly underlie the individual variations commonly observed in inbred mouse models of disease.

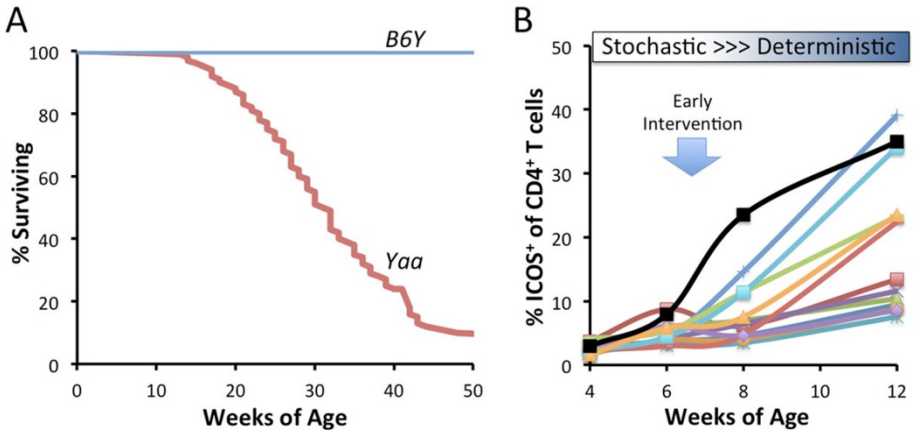

Figure 1(abstract A6) A, Considerable individual variation in the survival of BXSB. *Yaa* male mice, n = 93. Long term survival of 26 males carrying the C57BL/6 Y chromosome (*B6Y*) demonstrate the dependency of the autoimmune disease on *Yaa*. **B**, Longitudinal phenotyping of a cohort of BXSB. *Yaa* mice for $ICOS^+$ $CD4^+$ T cells. Each line represents data from FACS analysis of blood white blood cells from individual mice. Transition from stochastic to deterministic occurs at 6-8 weeks of age. Therapies applied at this point are predicted to have the potential of preventing this transition.

However, such variation is usually disregarded. Conventional experimental studies are usually designed to override "stochastic noise" by attempts to size comparator cohorts with sufficient discriminative power to override individual variability. When significance in cohort comparisons is not achieved, the null hypothesis is invoked. The individual variability within genetically matched cohorts is an untapped source of biological information that can inform causal mechanisms of disease.

Extrapolation to disease prognosis and early interventions in humans: Variation in the severity and presentation among individuals diagnosed with a human autoimmune disease is the rule rather than the exception. While genetic risk and environment factors are certain to play important parts, the considerable phenotypic variation described above underscores the potential for stochastic behaviors to contribute significantly to disease variation. Genetically and environmentally fixed BXSB.*Yaa* mice exhibit patterns that are consistent with stochastic events giving rise to key deterministic events at the inception of autoimmune disease. By extrapolation, therapeutic interventions designed to abrupt such early fate decisions may head off lupus at its inception and have enduring effects on overall disease pathogenesis (Figure 1B).

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A7

DNA repair in lupus

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Background: The myriad of mouse genetic alterations that result in a lupus-like phenotype and the >100 genes now known to be involved in human lupus are all probably only a hint at the potential complexity of the many mechanisms that lead to systemic lupus erythematosus (SLE).
Methods: We have applied exome sequencing to 24 SLE patients and their parents (trios) in an effort to conquer the data analysis and to identify candidate genes that may contribute when the activity of their gene products were substantially altered.
Results: The proband of one of our SLE trios had *de novo* mutations in *RAD54B* that was predicted to change ARG to GLN and to be severely damaging to protein product activity by multiple algorithms. A second much more conservative *de novo* mutation in *DOCK8* was not predicted to be consequential. *RAD54B* is a component of the homologous recombination DNA repair pathway. Cells from the SLE proband were unusually sensitive to ionizing radiation by the colony survival and comet tail assays. Ionizing radiation selectively induced interferon responsive genes in cells from this patient and not from controls. Transfection of the wild-type gene into the cells from this patient led to overexpression of the *RAD54B* gene product and returned ionizing radiation resistance toward normal.
Conclusion: These data in addition to the other five other genes directly or indirectly involved in altering risk of SLE by influencing DNA repair (*TREX1, RAD51B, XRCC1, XRCC3*, and *XRCC4*) implicate base excision repair, nonhomologous end joining, and homologous recombination. These results suggest that multiple DNA repair mechanisms contribute to SLE susceptibility.

A8

Impact of genetic variants on B-cell development and function in systemic lupus erythematosus

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Arthritis Research & Therapy 2014, **16(Suppl 1):**A8

Background: Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by the progressive loss of tolerance to nuclear antigens and the production of pathogenic autoantibodies. Genetic polymorphisms in genes involved in B-cell signaling, *PTPN22, CSK, BLK* and *BANK1*, are associated with susceptibility to SLE.
Methods: We have utilized a cohort of genotyped healthy subjects to better understand how these genetic variants contribute to the failure of B-cell tolerance seen in SLE. PBMC from these subjects are analyzed using multiparameter flow cytometry to assess the composition of the B-cell compartment and the response of B cells to stimulation via BCR and CD40.
Results: Our studies in healthy subjects who carry this variant have demonstrated alterations in the composition of the transitional and naïve B-cell pool. This is functionally correlated with the altered BCR response and enhanced survival of these cells in carriers of the risk variant. Three potentially functional *BANK1* SNPs (including a splice branch point-site variant and two coding variants) are associated with SLE. We have shown that the *BANK1* risk variants are associated with homeostatic changes in the peripheral B-cell pool that include a significant expansion of the total memory and preswitch memory compartment; and a significant decrease in

naïve B cells in subjects homozygous for the *BANK1* risk alleles. In further studies we have demonstrated that the *BANK1* splice variant is associated with significantly reduced expression of the Δ2 isoform and that the risk haplotype is further associated with blunted proximal BCR signaling in naïve B cells and enhanced p-AKT in memory B cells. Studies are ongoing to investigate the impact of the *BANK1* variant on plasma cell differentiation.
Conclusions: Studies of healthy subjects who carry SLE risk genes demonstrate alterations in B-cell function and fate. These studies can then be extended to subjects with SLE to understand how these genetic variants impact B-cell development and tolerance in the setting of disease.

A9

Differential methylation of interferon-related genes is associated with autoantibody production in systemic lupus erythematosus

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Background: DNA methylation, an epigenetic modification, influences gene expression and has been implicated in the pathogenesis of systemic lupus erythematosus (SLE). Two recent studies suggest that interferon-regulated genes are hypomethylated in SLE patients compared with unaffected controls. However, these studies have not examined whether DNA methylation is associated with specific disease manifestations. The goal for the current study was to determine whether differential DNA methylation is associated with autoantibody production in SLE, with a focus on the anti-dsDNA autoantibody.
Methods: The methylation status of 467,314 CpG sites across the genome was characterized for 326 women with SLE. Associations between anti-dsDNA autoantibody production and methylation status was assessed using a discovery and replication study design. Multivariable regression was used to adjust for confounders including estimated leukocyte cell proportions and population substructure. In secondary analyses, we assessed differential methylation associations with anti-SSA, anti-Sm, and anti-RNP autoantibody production.
Results: Significant associations between anti-dsDNA autoantibody production and methylation status were replicated for 16 CpG sites ($P_{discovery} < 1.07 \times 10^{-7}$ and $P_{replication} < 0.0029$) in 11 genes. The adjusted mean difference in methylation between the two autoantibody subgroups ranged from 1 to 19%, and the adjusted odds ratio for anti-dsDNA autoantibody production comparing the lowest with the highest tertile of methylation ranged from 6.8 to 18.2. Differential methylation for these sites was also associated with anti-SSA, anti-Sm, and anti-RNP autoantibody production. All associated sites were less methylated in autoantibody-positive compared with autoantibody-negative cases. Seven of the 11 associated genes either induce interferon or regulate the interferon signaling pathway. Among the differentially methylated genes associated with the production of at least one autoantibody, cytokine and interferon signaling pathways were the most represented.
Conclusions: Hypomethylation of interferon-related and other genes is associated with autoantibody production among SLE cases. Differential methylation of these 11 genes in autoantibody-positive SLE cases may explain their recently reported associations with SLE risk, and the extent of hypomethylation may influence disease manifestations.

A10

Subphenotype mapping in systemic lupus erythematosus identifies multiple novel loci associated with circulating interferon alpha

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Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by inflammation of multiple organ systems, loss of tolerance to self-antigens, and dysregulated interferon responses. SLE is both genetically and phenotypically heterogeneous, and we hypothesize that this greatly reduces the power of overall case-control studies in SLE. Increased circulating level of the cytokine interferon alpha (IFNα) is a stable, heritable trait in SLE which has been implicated in primary disease pathogenesis. Forty to 50% of patients have high IFNα, and high levels correspond with clinical differences.
Methods: To study genetic heterogeneity in SLE, we performed a case-case study comparing patients with high versus low IFNα in over 1,800 SLE cases. Four hundred European ancestry cases formed the discovery GWAS set, and 1,443 cases from a large independent multi-ancestral replication cohort were used to validate associations.
Results: In meta-analysis, the top associations in European ancestry were PRKG1 rs7897633 ($P_{Meta} = 2.75 \times 10^{-8}$) and PNP rs1049564 ($P_{Meta} = 1.24 \times 10^{-7}$). We also found evidence for cross-ancestral background associations with the *ANKRD44* and *PLEKHF2* loci. These loci have not been previously identified in case-control SLE genetics studies. Bioinformatic analyses implicate these loci functionally in dendritic cells and natural killer cells, both of which are involved in IFNα production in SLE.
Conclusions: As case-control studies of complex heterogeneous diseases reach a limit of feasibility with respect to subject number and detectable effect size, the study of informative pathogenic subphenotypes becomes a highly attractive and efficient strategy for genetic discovery in complex human disease.
Acknowledgements: SNK and YG-P contributed equally to the manuscript.

A11

Fine mapping and functional study of the systemic lupus erythematosus-associated *NMNAT2/SMG7* locus

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Background: *NMNAT2* (rs2022013 located at intron 1) was identified as a SLE risk locus in a European-derived population in a genome-wide association study (GWAS). *NMNAT2* (nicotinamide mononucleotide adenylyltransferase 2) is expressed mainly in the brain, regulating energy metabolism. Proximal to the SLE-associated *NMNAT2* variant is *SMG7*, encoding a component of the mRNA quality control pathway that regulates spliceosomal machinery such as Sm and snRNP via alternative splicing. We fine mapped the *NMNAT2/SMG7* region in multiple ancestries and explored functional consequences of the identified variants.
Materials and Methods: We genotyped/imputed 313 SNPs covering an ~550 kb *NMNAT2/SMG7* region in 15,424 case-control subjects from European-Americans (EA), African Americans, Asians and Amerindian/Hispanics, assessed SNPs for association with SLE using a logistic regression model adjusted for sex and ancestry, and used haplotype-based conditional testing to distinguish independent associations. Quantitative real-time PCR and luciferase reporter assays were used to examine allelic differences in *SMG7* expression and transcription activity. PBMCs from SLE patients (n = 13) were cultured with or without siRNA targeting *SMG7, GAPDH* (positive control) or siRNA with a nontargeting sequence (NC, negative control), and culture supernatants were measured by ELISA for levels of antinuclear antibody (ANA) and cytokines/chemokines.
Results: We confirmed association at rs2022013 and identified two independent signals in EA only: intron 1 of *NMNAT2* tagged by rs12146097

($P = 1.5 \times 10^{-10}$, OR = 1.38); and multiple *SMG7* SNPs tagged by rs2275675 ($P = 5.7 \times 10^{-8}$, OR = 1.22). Expression quantitative trait locus data showed SLE-risk alleles of *NMNAT2/SMG7* variants consistently associated with decreased mRNAs of *SMG7*, but not *NMNAT2*, in cell lines, suggesting *SMG7* is a more likely risk gene for SLE. The rs2275675 risk allele was associated with decreased *SMG7* mRNAs dose dependently in PBMCs of 86 SLE patients and 119 controls ($P = 0.001$ and 6.84×10^{-8}, respectively), and reduced transcription activity in two transfected cell lines ($P \leq 0.004$). *SMG7* mRNA levels in PBMCs correlated inversely with ANA titers in 68 SLE patients ($P = 0.0089$, $r = -0.31$). Compared with culture supernatants of SLE PBMCs treated with NC-siRNA, those treated with *SMG7*-siRNA showed increased ANA ($P < 0.0001$) and CCL19 ($P = 0.0002$; a ligand for CCR7 promoting movement/ interaction of B-Th cells and antibody production).
Conclusions: We confirmed the previous GWAS *NMNAT2* association and identified independent *SMG7* association with SLE in an EA population. The SLE-risk alleles are dose-dependently associated with decreased *SMG7* mRNAs, and *SMG7* reduction increases ANA and CCL19 production in PBMC cultures of SLE patients, suggesting that dysfunction in mRNA surveillance conferred by SLE-associated *SMG7* variants contributes to SLE manifestations.

A12

Impact of provider specialty on the diagnosis and management of systemic lupus erythematosus in the American Indian/Alaska Native population

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Background: Systemic lupus erythematosus (SLE) is a complex disease that is traditionally diagnosed and managed by specialists, typically rheumatologists. Higher SLE prevalence in racial/ethnic minorities such as American Indian/Alaska Native (AI/AN) people, often residing in areas with less access to rheumatologists, may necessitate diagnosis and management of SLE by primary care providers (PCP) in some cases. The purpose of this analysis was to identify areas of potential difference between PCP and specialist diagnosis and management of SLE in a population-based lupus registry of AI/AN people.
Methods: All individuals with SLE meeting our inclusion criteria were selected from the 2009 Indian Health Service lupus registry population. Inclusion in this analysis was limited to individuals with a final diagnosis of SLE made by a PCP or specialist (dermatologist, nephrologist or rheumatologist) and documented in the medical record. Based on medical record abstraction, SLE classification criteria were validated for each individual. Testing for biologic markers of SLE and medication use at any time during the course of the disease was also abstracted.
Results: Of the 320 patients identified with a documented physician diagnosis of SLE, 71 had been diagnosed by a PCP. SLE diagnosis by a specialist was associated with a higher median number of American College of Rheumatology (ACR) classification criteria (5 vs. 2), a higher percentage of patients meeting the definition of SLE by ACR criteria (79% vs. 22%), the Boston Weighted criteria (82% vs. 32%), and an abridged version of the Systemic Lupus International Collaborating Clinics criteria (83% vs. 35%) ($P < 0.001$ for all comparisons). Additionally, specialist diagnosis was associated with an increased proportion with any testing for anti-double-stranded DNA antibody (93% vs. 73%) and complement C3 and C4 (84% vs. 52%) documented in the medical record ($P < 0.001$ for all). Lastly, specialist diagnosis was associated with ever treatment with hydroxychloroquine (86% vs. 64%, $P < 0.001$) as documented in the medical record at any time during their disease course.
Conclusions: Within the population studied, specialist diagnosis of SLE was associated with a higher number of SLE classification criteria met, a higher percentage of patients tested for biomarkers of disease, and a higher percentage of patients ever treated with hydroxychloroquine.

A13

Racial discrimination and disease damage among African American women with systemic lupus erythematosus

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Background: African American women with SLE experience faster progression and worse consequences of disease compared with their White counterparts. This study sought to examine whether self-reported routine experiences of discrimination, as a source of psychosocial stress, is associated with disease damage among African American women with SLE.
Methods: Participants were 578 African American women in the Georgians Organized Against Lupus study, a population-based cohort of SLE patients in Atlanta, GA, USA. Disease damage was assessed using the Self-Administered Brief Index of Lupus Damage (SA-BILD), a validated, patient-reported measure of organ damage since the onset of SLE. Discrimination was assessed using the Everyday Discrimination Scale, a widely used measure of routine experiences of unfair treatment. Ordinary least-squares regression analyses were used to examine the outcome of SA-BILD score by the primary predictors: unfair treatment, racial discrimination attribution, and their interaction, controlling for age and years since SLE diagnosis.
Results: The average SLE damage score in our sample was 2.3 (SD = 2.4), and the mean years since initial diagnosis was 13.6 years (SD = 9.3). The mean unfair treatment score was 1.92 (SD = 0.95), indicating that on average participants reported experiencing each of the forms of unfair treatment approximately once a year. A total of 159 participants (27.6%) reported not experiencing any unfair treatment. Among participants reporting any unfair treatment, most did not make an attribution of racial discrimination ($n = 258$ compared with $n = 146$). Age ($r = 0.23$, $P < 0.001$) and years since diagnosis ($r = 0.25$, $P < 0.001$) were significantly correlated with SLE damage. Reports of unfair treatment and making an attribution to racial discrimination were not significantly associated with SLE damage. In multivariable regression analyses controlling for age and years since diagnosis, we found a significant interaction between unfair treatment and attributions to racial discrimination ($b = -0.52$, SE = 0.24, $P = 0.03$). Greater unfair treatment attributed to nonracial causes was associated with higher SA-BILD score, whereas unfair treatment attributed to race showed an inverse association (Figure 1).
Conclusions: This study highlights the role that social stressors have in contributing to the progression of SLE and is the first to examine whether unfair treatment and racial discrimination are associated with disease damage among African American women with SLE. Consistent with findings from studies on discrimination and other health outcomes, these results suggest more complex, interactive rather than direct associations with SLE damage, with differential relationships being found between those who attributed unfair treatment primarily to racial discrimination versus those who did not.

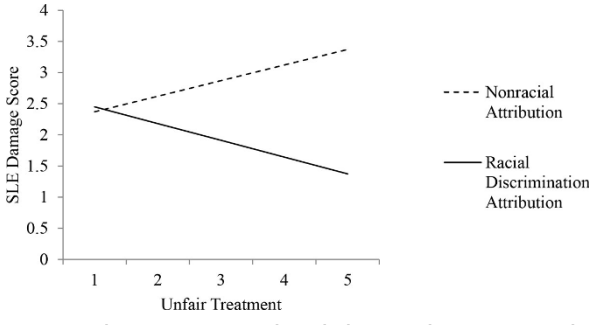

Figure 1(abstract A13) Predicted disease damage score by attribution to racial discrimination among African American women with systemic lupus erythematosus (SLE) reporting any unfair treatment in the Georgians Organized Against Lupus (GOAL) study ($n = 578$; 2011 to 2012).

A14

The Scleroderma Patient-centered Intervention Network for conducting large-scale international trials of nonpharmacological interventions in scleroderma: a way ahead for lupus?

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Background: Psychosocial and rehabilitation interventions are increasingly used to attenuate disability and improve health-related quality of life (HRQL) in chronic diseases, but are typically not available for patients with less common diseases such as scleroderma or lupus. Conducting rigorous, adequately-powered trials of nonpharmacological interventions for patients with rare diseases is difficult. The Scleroderma Patient-centered Intervention Network (SPIN) is an international collaboration of patient organizations, clinicians, and researchers. The aim of SPIN is to develop a research infrastructure to test accessible, low-cost self-guided online interventions to reduce disability and improve HRQL for people living with scleroderma. Once tested, effective interventions will be made accessible through patient organizations partnering with SPIN.
Methods: SPIN will utilize a novel research design, the cohort multiple randomized controlled trial (cmRCT) design, to collect longitudinal data related to problems experienced by people living with scleroderma and as a framework for developing, evaluating, and delivering psychosocial and rehabilitation interventions. In the cmRCT design, patients consent to participate in a cohort for ongoing data collection. The aim is to recruit 1,500 to 2,000 patients from centers across the world within a period of 5 years (2014 to 2018). Eligible participants are persons ≥18 years of age with a verified diagnosis of scleroderma. In addition to baseline medical data, participants will complete patient-reported outcome measures every 3 months. Upon enrolment in the cohort, patients will consent to be contacted in the future to participate in intervention research and to allow their data to be used for comparison purposes for interventions tested with other cohort participants. Once interventions are developed, patients from the cohort will be randomly selected and offered interventions as part of pragmatic RCTs. Outcomes from patients offered interventions will be compared with outcomes from trial-eligible patients who are not offered the interventions.
Discussion: The use of the cmRCT design, the development of self-guided online interventions, and partnerships with patient organizations will allow SPIN to develop, rigorously test, and effectively disseminate psychosocial and rehabilitation interventions for people with scleroderma. A similar approach could be used to develop and test psychosocial and rehabilitation interventions for people with lupus.

A15

Linking anti-Ro antibodies to fibrosis in congenital heart block: translation to a clinical trial

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Background: One of the strongest clinical associations with autoantibodies (Ab) directed to components of the SSA/Ro-SSB/La ribonucleoprotein complex is the development of congenital heart block (CHB) in an offspring. Fetal disease is independent of maternal disease and often anti-Ro Ab are first sought only because CHB has been identified. The first-time risk of 2% is 10-fold higher in women who have had a previous CHB child. Tissue injury in the fetus is presumed to be dependent on the FcγR-mediated transplacental passage of maternal IgG Ab. Despite attempts of large multicenter studies to forestall disease by careful monitoring, irreversible block and extensive myocardial injury have been documented within 7 days of a normal rhythm and PR interval. *In vivo* and *in vitro* data support that cardiac fibrosis may be consequent to macrophage Toll-like receptor (TLR) signaling following ligation of the ssRNA complexed to the Ro protein. TLR signaling and fibrotic endpoints may be abrogated by chloroquine (CQ), which inhibits endosomal acidification. This *in vitro* observation was initially "translated" to patients by evaluating the use of hydroxychloroquine (HCQ) in an extensive case-control retrospective chart review of anti-Ro/La Ab exposed fetuses of mothers with SLE enrolled in three databases. This approach was followed by another study that addressed whether HCQ use reduces the expected recurrence rate of CHB. The collective results were highly encouraging.
Methods and results: Based on these studies we initiated an open-label prospective study design using Simon's two-step approach. HCQ at 400 mg is initiated by 10 weeks following conception. Serial echocardiograms (monitor PR interval) and evaluation of maternal and cord blood biomarkers (HCQ levels, IFNα signatures, and Ab titers) are part of the protocol to address maternal compliance, pathobiology and efficacy. The first stage has been completed with 19 subjects and only one recurrence of CHB.
Future directions: Over the next 4 years, 35 subjects will be enrolled. Ultimately, HCQ will be considered efficacious for the prevention of CHB if fewer than six cases occur among a total of 54 subjects evaluated. A positive result will probably change the management of all anti-Ro-positive women who have had a previous child with CHB and illustrate the importance of translational science. Perhaps most relevant to impact, a potential prevention would justify screening of all pregnant women for anti-Ro antibodies, particularly relevant since mothers of affected children are frequently asymptomatic, a point critical to early pregnancy counseling.

A16

Targeting IRF5 inhibition in human B cells: identification of new functional roles that implicate IRF5 in systemic lupus erythematosus B-cell pathology

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Background: The interferon regulatory factor 5 (*IRF5*) systemic lupus erythematosus (SLE) risk loci is considered one of the most strongly and consistently associated SLE loci identified. It has been detected using both candidate gene and genome-wide association studies. Haplotypes are associated with increased, decreased, or neutral levels of risk for SLE and have been shown to associate with functional changes in IRF5-mediated signaling, including increased expression and elevated IFNα activity. The majority of studies, however, were performed in peripheral blood mononuclear cells and thus little is known of the function of IRF5 in specific human immune cell populations. We are interested in understanding the role of IRF5 in human B cells since previous studies in mice implicated a role for IRF5 in effector B-cell development and function and murine models of lupus lacking the *Irf5* gene showed reduced ANA, glomerulonephritis and pathogenic autoantibody production. Unfortunately, many of these studies were complicated by the finding of a secondary mutation in the *Dock2* gene amongst $Irf5^{-/-}$ mice. Recent findings from our laboratory indicate that IRF5 is constitutively localized to the nucleus of human SLE memory B cells and that activation of healthy donor B cells results in IRF5 nuclear localization, suggesting a functional role for IRF5 in human B cells.
Methods: Human immortalized and primary B cells were utilized in this study. Primary naïve B cells were obtained by informed consent at University Hospital, Newark, NJ, USA under an approved IRB protocol, and either mock stimulated or stimulated with anti-IgM and CpG-B for activation. B-cell development, cytokine expression, autoantibody production and class switch recombination were examined in the presence or absence of siRNAs targeting IRF5 expression or peptide inhibitors targeting IRF5 nuclear localization. An IRF5-mediated B-cell signature was also examined under similar experimental conditions by ChIP-seq analysis.
Results: We find that IRF5 is indeed important for human B-cell effector functions, including, but not limited to, cytokine expression, differentiation, and autoantibody production, and have identified a pro-effector B cell gene program that is regulated by IRF5.
Conclusions: These findings show for the first time that IRF5 is an important regulator of human effector B-cell development and function

and thus, when overexpressed or overactivated, as seen in SLE B cells, would be expected to contribute significantly to SLE B-cell pathology. These data provide initial insight into how inhibitors of IRF5 activation may change SLE disease onset and/or progression.

A17

Platelet-derived microparticles serve as an important source of autoantigens and discriminate between levels of disease activity in systemic lupus erythematosus

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Background: Immune complexes (IC) are implicated in the pathogenesis of several autoimmune diseases including systemic lupus erythematosus (SLE). In SLE, submicron extracellular vesicles, called microparticles (MP), are thought to serve as an antigenic surface promoting the deposition of immunoglobulins and the formation of MP-associated immune complexes (mpICs). However, the cellular origin of these mpICs is unknown and whether they correlate with disease activity and particular clinical features remains to establish.
Methods: The concentrations of mpICs in platelet-poor plasma from 193 women with SLE were determined using high-sensitivity flow cytometry. Considering the recently revealed role of platelets in SLE, we further scrutinized the contribution of platelets to mpICs formation. The platelet and nonplatelet MPs and mpICs were tested for association with lupus disease activity, damage, history of previous arterial disease, and the carotid intima-media thickness and plaque area on ultrasound. To assess whether disease activity and damage are associated with levels of MPs and mpICs, univariate and multivariate negative binomial models were built using the SLE disease activity index 2000 (SLEDAI-2K) and the SLICC/ACR damage index (SDI) as outcome variables. In all models, the predictor variable was the level of MPs or mpICs. When necessary, models were adjusted for covariables such as age, disease duration, menopausal status, hypertension, diabetes, anticoagulant or antiplatelet medication, antimalarial medication, prednisone use, smoking status, and ethnicity.
Results: The clinical characteristics of the 193 women studied were: age (mean (SD)) 46.3 (14.7) years; disease duration 18.5 (12.0) years; ethnicity (% Caucasian) 57%; ever-smoker 34%; menopausal in 55%; hypertensive 30%; diabetic 5%; prescribed anticoagulant or antiplatelet medication 25%; prescribed antimalarial medication 74%; prescribed prednisone 44%. Univariate analyses for activity revealed that platelet-derived mpICs, but not mpICs from other cells, were associated with SLEDAI-2K. In the multivariate model, this association remained significant ($P = 0.02$ for annexin V^+ platelet mpICs and $P = 0.0006$ for annexin V^-platelet mpICs) after adjusting for disease duration, hypertension and currently on prednisone. There was no association between platelet mpICs and SDI.
Conclusions: Platelet-derived MPs are a major source of autoantigens serving mpIC formation in SLE. Platelet-derived mpICs are associated with lupus disease activity level on the SLEDAI-2K but not with damage. This is the first report of an association between platelet mpICs and clinical marker of activity in SLE and in any autoimmune disease. Platelet mpICs need to be further considered as a possible biomarker of lupus disease activity.
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A18

Vimentin is a dominant target of *in situ* humoral immunity in human lupus tubulointerstitial nephritis

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Background: In lupus nephritis (LuN), severe tubulointerstitial inflammation (TII) predicts progression to renal failure. Severe TII is associated with tertiary lymphoid neogenesis and *in situ* antigen-driven clonal B-cell selection. The dominant autoantigen(s) driving *in situ* B-cell selection in TII are not known.
Methods: Single $CD38^+$ or Ki-67^+ B cells were laser captured from seven LuN biopsies. Twenty clonally expanded immunoglobulin heavy and light chain variable region pairs were cloned and expressed as antibodies. Seven more antibodies were cloned from flow-sorted $CD38^+$ cells from an eighth biopsy. Antigen characterization was performed using a combination of confocal microscopy, ELISA, screening protoarrays, immunoprecipitation and mass spectrometry. Serum IgG titers to the dominant antigen were determined in 45 LuN and 38 non-nephritic lupus samples using purified antigen-coated arrays. Autoantigen expression was localized by immunohistochemistry and immunofluorescence on normal and LuN kidney.
Results: Thirteen of 27 antibodies reacted with cytoplasmic structures, four reacted with nuclei and none with dsDNA, Sm or RNP. Vimentin was the only autoantigen identified by both mass spectrometry and on protoarray. Eleven anticytoplasmic TII antibodies directly bound vimentin. Vimentin was highly expressed by tubulointerstitial inflammatory cells, and tested TII antibodies preferentially bound inflamed tubulointerstitium. Finally, high titers of serum anti-vimentin antibodies were associated with severe TII ($P = 0.0001$).
Conclusions: Vimentin, an antigenic feature of inflammation, is a dominant autoantigen targeted *in situ* in LuN TII. This adaptive autoimmune response probably feeds forward to worsen TII and renal damage.

A19

Aggregation of MAVS antiviral protein suggests a mechanism for increased type I interferon production in SLE

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Background: Patients with systemic lupus erythematosus (SLE) often have increased type I interferon levels (IFN-I) and activation of IFN-inducible genes (IFN signature). Because IFN-I has a key role in both the innate and adaptive immune responses, it is believed that heightened levels of this cytokine and the many genes it regulates may underlie the immune hyperreactivity and autoimmunity of SLE. The mechanism of IFN-I hyperproduction in SLE is under intense study. An important lead has emerged from our laboratory implicating the RIG-I antiviral pathway as a possible cause. In particular, the mitochondrial adaptor protein MAVS is a key intermediary in the RIG-I/MDA5 pathway, where viral RNA triggers a conformational change in RIG-I, leading to MAVS activation with subsequent IFN production. It has been reported that MAVS may form large prion-like aggregates, which might stimulate IFN-I production in a potent and prolonged fashion. We wondered whether such aggregates might be detectable *ex vivo* in SLE patients, and whether they might play a role in the sustained increased production of IFN-I.
Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from patients fulfilling ACR criteria for SLE, from healthy controls, and from patients with rheumatoid arthritis (RA). Mitochondrial lysates were prepared and MAVS aggregation was identified with a semi-denaturing agarose gel and confirmed by confocal immunofluorescent microscopy.
Results: Twenty-two of 61 SLE patients showed clear MAVS aggregation, with essentially all of their MAVS protein in a high molecular weight aggregated form. None of the RA patients and only three of 33 healthy controls had abnormal MAVS. Clinical data analysis revealed that 82.4% MAVS-aggregate-positive SLE patients (mean age 46) had anti-SSA antibodies, compared with 40% MAVS-aggregate-negative patients (mean age 44), $P < 0.01$ by chi-square. 64.7% aggregation-positive patients had active SLE disease (skin rash, arthritis, increased ESR, low C4, and active renal disease), while only 10% of the aggregation-negative patients had active disease.
Conclusions: Our findings are consistent with the notion that activation of the RIG-I pathway through inappropriate or persistent MAVS aggregation may lead to increased IFN-I production, immune stimulation, and systemic autoimmunity in SLE.

A20

Aberrant expansion of CXCR5$^+$ memory CD4 T cells in patients with systemic lupus erythematosus

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Background: Autoreactive B cells in SLE undergo autoantigen selection, suggesting a requirement for germinal center follicular helper T (Tfh) cells in their maturation. However, evidence for dysregulation of Tfh cells in SLE and their potential contribution to disease remains unclear. Recently, blood CXCR5$^+$ CD4 T cells, a heterogeneous pool consisting of functionally distinct Th1-like, Th2-like, and Th17-like subsets, have been proposed to be the circulating (blood) memory Tfh cells. We hypothesized that expanded CXCR5$^+$ memory cells in the blood of human lupus patients promote B-cell helper function reflecting the abnormal T-B-cell responses in secondary lymphoid organs.
Methods and results: We characterized such cells in SLE patients by flow cytometry and T-B coculture studies. SLE patients had significant expansion of CXCR5$^+$ICOS^{hi}PD-1^{hi} CD4 T cells compared with controls. Such cells were Bcl6$^-$, but robustly expressed IL-21 with a portion Ki-67$^+$, indicating their functional activity. The blood cells were capable of providing blood-born memory B cells with survival and differentiation signals to secrete isotype switched Igs, including antinuclear antibodies.
Conclusions: We speculate that therapies which alter T-B collaboration in lupus will abrogate their expansion, accompanied by reduced autoantibody titers and improved disease activity in SLE patients. Our results suggest that aberrant T-B collaboration in lupus is critical to disease pathogenesis and its blockade is likely to be important therapeutically.
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A21

Identification of stage-specific genes associated with lupus nephritis and response to remission induction in NZB/W and NZM2410 mice

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Background: Lupus nephritis affects 30 to 70% of systemic lupus erythematosus (SLE) patients and its treatment remains insufficiently effective and excessively toxic. Although biomarkers for nephritis are being identified there is still no reliable way of predicting an impending renal flare or determining which patients will respond to therapy. Because human renal tissue cannot be obtained sequentially during remission and relapse, animal models are often used to study progression of lupus nephritis. To elucidate the molecular mechanisms involved in renal inflammation during the progression, remission and relapse of nephritis we performed a transcriptome analysis of renal tissue from two murine lupus models, NZB/WF1 mice that develop proliferative glomerulonephritis and NZM2410 mice that develop glomerulosclerosis with minimal inflammation.
Methods: Kidneys from NZB/W F1 and NZM2410 mice were harvested at intervals during their disease course or after remission induction with either combination cyclophosphamide/costimulatory blockade or with BAFF inhibition. Genome-wide expression profiles were obtained from microarray analysis of perfused kidneys. Real-time PCR analysis for selected genes was used to validate the microarray data. Comparisons between groups using SAM, and unbiased analysis of the entire dataset using singular value decomposition and self-organizing map were performed.
Results: Few changes in the renal molecular profile were detected in pre-nephritic kidneys but a significant shift in gene expression, reflecting inflammatory cell infiltration and complement activation, occurred at proteinuria onset. Subsequent changes in gene expression predominantly affected mitochondrial dysfunction and metabolic stress pathways. Remission induction reversed most, but not all, of the inflammatory changes and progression towards relapse was associated with recurrence of inflammation, mitochondrial dysfunction and metabolic stress signatures. Endothelial cell activation, tissue remodeling and tubular damage were the major pathways associated with loss of renal function.
Conclusions: Immune cell infiltration and activation is associated with proteinuria onset and reverses with immunosuppressive therapy but disease progression is associated with renal hypoxia and metabolic stress. Optimal therapy of SLE nephritis may therefore need to target both immune and nonimmune disease mechanisms. In addition, the overlap of a substantial subset of molecular markers with those expressed in human lupus kidneys suggests potential new biomarkers and therapeutic targets.
Acknowledgements: RB and CCB contributed equally.

A22

Blimp-1 and systemic lupus erythematosus

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Our laboratory has been studying the impact of low Blimp-1 expression on dendritic cell function in SLE, analyzing both a mouse model of SLE in which there is a deletion of Blimp-1 in CD11c dendritic cells (DC Blimp-1^{KO} mice) and healthy individuals with the SLE risk allele of Blimp-1. This allele leads to reduced Blimp-1 expression in dendritic cells. Low expression of Blimp-1 alters cytokine expression following TLR activation and antigen-processing machinery. This leads to a highly distinct TCR repertoire in T-follicular helper cells in DC Blimp-1^{KO} mice. Much of this phenotype is under estrogen regulation. These data therefore provide an integrated explanation for altered cytokines, autoantibodies and female predisposition in SLE.

A23

A role for cutaneous gamma delta T cells in the development of systemic lupus erythematosus

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Background: Ultraviolet (UV) light exposure promotes the development of cutaneous lupus and can induce flares of systemic lupus erythematosus. Similarly, UV light can induce lupus in genetically prone strains of mice. Nonobese diabetic (NOD) mice prone to autoimmune disease demonstrate lupus-like disease after repeated combined UV irradiation and topical application of TLR-7 agonist imiquimod (IMQ). In contrast, repeated topical application of a Toll-like receptor (TLR) 7/8 agonist promotes psoriasiform skin lesions in nonautoimmune mice such as Balb/c. The cellular and molecular determinants of these processes are still unknown.
In this study we have compared the skin lesions induced by repeated topical IMQ in Balb/C *VS* NOD mice. Gamma delta T cells are innate immune cells that bridge innate and adaptive immunity in part by modulating dendritic cell maturation. We have thus explored the role of gamma delta T cells in the induction of psoriasis and SLE following topical TLR 7/8 agonist application.
Methods: NOD and Balb/C mice received 70 mg topical IMQ 5% cream on shaved back skin daily for 5 days. Skin, draining lymph nodes (LNs) and sera were obtained for histological and serological analysis.
Results: Balb/c mice but not NOD mice developed thickened erythematous and scaly skin lesions similar to psoriasis. Histological examination revealed acanthosis, parakeratosis and papillomatosis resembling psoriasis in Balb/c mice but not in NOD mice. IL-17-producing T cells were increased in the dermis and skin draining LNs of Balb/C mice after 5 days topical IMQ, whereas the frequency of IFNγ-producing gamma delta T cells was higher in NOD mice. Serum collected 24 hours after treatments with IMQ showed

elevation of Th1 cytokines in NOD mice, but not in Balb/C mice. Repeated IMQ increased the relative frequencies of granulocytes in the skin and skin draining LNs in Balb/c but not in NOD mice. In contrast, the frequency of macrophages was increased in NOD skin.
Conclusions: Our work suggests that a predominant Th1 response, orchestrated in part by gamma delta T cells in response to TLR7/8 agonism in the skin, may predispose to SLE-like autoimmunity.

A24

Neutrophils - a complex story in the pathogenesis of systemic lupus erythematosus

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Background: Neutrophils have long been recognized as important contributors of inflammation and tissue destruction in systemic lupus erythematosus (SLE). The LE cell (engulfment of antibody-opsonized nuclear material by neutrophils) was for decades regarded as the hallmark of SLE. With the discovery of neutrophil extracellular traps (NETs), the extrusion of intracellular modified DNA and histones to trap microbes, as well as the highly proinflammatory neutrophil subset named low-density granulocytes (LDGs) during the last decade, interest in the neutrophil in SLE has seen a renaissance. However, there are data to suggest that neutrophils can play important roles in protection against, induction of and resolution of inflammation.
NETs were originally described as chromatin bound to granular and cytoplasmic molecules. However, today we know that the composition of NETs is highly dependent on the inducing stimulus and may contain characteristic lupus autoantigens such as DNA and chromatin. In SLE, LDGs spontaneously release NETs *ex vivo*, and *in vitro*, and autoantibodies directed against RNP induce release of neutrophil DNA able to subsequently mediate interferon (IFN)-alpha production by plasmacytoid dendritic cells (pDCs). Due to the suggested role of NETs in exposing autoantigens and supporting type I IFN production, several attempts have been made to inhibit NETosis in murine lupus models. So far, two main pathways - citrullination and oxidation - have been targeted. Whereas inhibition of the citrullination pathway (PAD4) reduced development of nephritis, deficiency in oxidation (Nox2) resulted in worsened lupus-like disease.
Methods and results: We have studied the interplay between neutrophils and peripheral blood mononuclear cells (PBMCs) with regard to production of inflammatory mediators in response to nucleic acid-containing immune complexes (ICs). As demonstrated previously, RNA-containing ICs are efficient inducers of type I IFNs by either isolated pDCs or pDCs in PBMCs. However, when NETosis was induced by SLE ICs in the presence of PBMCs, production of type I IFNs, as well as other inflammatory cytokines, was markedly inhibited. This somewhat surprising finding may be explained by an inability of NETs to induce substantial inflammation in blood cultures due to the recently demonstrated anti-inflammatory effects through trapping and degradation of proinflammatory cytokines. In addition, neutrophils may compete for IC binding and internalization.
Conclusions: We thus propose that in a physiological setting with the presence of both neutrophils and PBMCs, neutrophils may act as a sentinel capable of directing proinflammatory or anti-inflammatory responses depending on the presence of other cell types, spillage of NETs and other factors.

A25

mTOR activation triggers proinflammatory expansion of IL-4-producing and necrosis-prone double-negative T cells, precedes flares, and serves as target for treatment in patients with systemic lupus erythematosus

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Background: Oxidative stress is increased in systemic lupus erythematosus (SLE), and it contributes to immune system dysregulation and fatal comorbidities. Mitochondrial dysfunction in T cells promotes the release of highly diffusible inflammatory lipid hydroperoxides, which spread oxidative stress to other intracellular organelles and through the bloodstream. In T cells from patients with SLE and animal models of the disease, glutathione, the main intracellular antioxidant, is depleted and the mechanistic target of rapamycin (mTOR), serine/threonine protein kinase, undergoes redox-dependent activation. In turn, reversal of glutathione depletion by application of its amino acid precursor, *N*-acetylcysteine, blocks mTOR activation and improves disease activity in lupus-prone mice and patients with SLE. While mTOR has been also recognized as an effector of T-cell lineage development, its role in autoimmunity and disease activation remain unclear.
Methods: Here, we prospectively examined mitochondrial dysfunction and mTOR in PBL relative to SLEDAI and BILAG disease activity indices during 274 visits of 59 patients and 54 healthy subjects matched for each patient blood donation. A total of 212 metabolic biomarkers and traditional biomarkers, anti-DNA, C3, and C4, were evaluated by partial least-square discriminant analysis (PLS-DA). False discovery rate (FDR) *P* values were determined for each contributing biomarker and considered significant at $P < 0.000236$ with correction for multiple comparisons (0.05/212). Medication use was compared between patient groups exhibiting flare and remission with chi-square and Fischer's exact tests.
Results: PLS-DA identified 15 of 212 parameters that accounted for 70.2% of the total variance and discriminated lupus and control samples ($P < 0.0005$); increased mitochondrial mass of $CD3^+/CD4^-/CD8^-$ double-negative (DN) T cells ($P = 1.1 \times 10^{-22}$) and FoxP3 depletion in $CD4^+/CD25^+$ T cells were top contributors ($P = 6.7 \times 10^{-7}$). Prominent necrosis and mTOR activation were noted in DN T cells during 15 visits characterized by flares (SLEDAI increase ≥4) relative to 61 visits of remission (SLEDAI decrease ≥4). mTOR activation in DN T cells was also noted at preflare visits of SLE patients relative to those of stable disease or healthy controls. DN lupus T cells showed increased production of IL-4, which correlated with depletion of $CD25^+/CD19^+$ B cells. Rapamycin treatment *in vivo* reduced SLEDAI and BILAG, blocked the IL-4 production and necrosis of DN T cells, increased the expression of FoxP3 in $CD25^+/CD4^+$T cells, and expanded $CD25^+/CD19^+$ B cells.
Conclusions: These results identify mTOR activation to be a trigger of IL-4 production and necrotic death of DN T cells, predictor of disease flares, and effective target for treatment in patients with SLE.
Acknowledgements: This work was supported in part by grants AI072648 and AT04332 from the National Institutes of Health, the Alliance for Lupus Research, and the Central New York Community Foundation [http://ClinicalTrials.gov:NCT00775476, http://ClinicalTrials.gov:NCT00779194].

A26

Elucidating the role of TNF-like weak inducer of apoptosis in the pathogenesis of cutaneous lupus

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Background: Cutaneous manifestations are very common in systemic lupus erythematosus (SLE). TNF-like weak inducer of apoptosis (TWEAK) is a soluble cytokine member of the TNF superfamily that binds to a sole receptor, Fn14. TWEAK/Fn14 signaling is involved in cell survival, apoptosis, cytokine production, and angiogenesis, and as such has been found to be important in both tissue repair and inflammatory diseases. Whether TWEAK is involved in autoimmune skin disease is not known.
Methods: To evaluate a possible role for TWEAK in the pathogenesis of cutaneous lupus, we generated a lupus-prone mouse strain, MRL-lpr/lpr (MRL/lpr), deficient in Fn14, and evaluated the development of skin disease in this strain as compared with age and gender-matched MRL/lpr mice. *In vitro* studies using a keratinocyte cell line, PAM212, were performed to evaluate the effects of TWEAK and ultraviolet B (UVB) irradiation on apoptosis and cytokine production.
Results: We found that lupus-prone MRL/lpr mice deficient for Fn14 (Fn14KO) had markedly attenuated cutaneous disease as compared with

Fn14WT mice. MRL/lpr Fn14KO mice had significantly less epidermal acanthosis and follicular plugging, and there was decreased infiltration of T cells and macrophages as compared with Fn14WT mice. *In vitro*, TWEAK treatment of murine keratinocytes stimulated the secretion of RANTES (via Fn14), and promoted apoptosis. Parthenolide decreased production of RANTES, indicating that this effect of TWEAK is mediated via NF-κB. Ultraviolet light, specifically UVB, is recognized as a potent trigger of cutaneous lupus. We found that TWEAK co-treatment exacerbates UVB light-induced keratinocyte apoptosis and increases the amount of RANTES secreted, when compared with cells treated with UVB alone. These synergistic effects of TWEAK+UVB on keratinocytes were probably due to upregulation of Fn14 expression by UVB.

Conclusions: Our data strongly implicate TWEAK/Fn14 signaling in the pathogenesis of the cutaneous manifestations of lupus.

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A27

Phenotypic consequences of TLR7-driven interferon and proinflammatory cytokine production in lupus

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Background: Although type I interferons (IFN-I) are involved in the pathogenesis of SLE, clinical heterogeneity of the disease is not fully explained by IFN-I overproduction. We investigated the relative importance of IFN-I versus proinflammatory cytokine production downstream of TLR7 in a murine lupus model and in SLE patients.

Methods: TLR7-mediated experimental lupus was induced in wild-type and knockout mice by pristane and the expression of IFN-I stimulated genes and numbers of plasmacytoid dendritic cells (pDCs) and inflammatory ($Ly6C^{hi}$) monocytes were assessed by PCR and flow cytometry, respectively. Production of TNFα and other proinflammatory cytokines was evaluated by intracellular staining. In parallel, we studied production of these cytokines in the bone marrow (BM) of SLE patients.

Results: SLE patients' BM exhibited striking death of niche and hematopoietic cells associated with local TNFα overproduction. BM from mice with pristane-induced lupus showed similar abnormalities. TNFα was produced mainly by BM neutrophils, many of which contained phagocytosed nuclear material (LE cells). TNFα production was abolished in $TLR7^{-/-}$ and µmt mice but was unaffected by C3 deficiency. Production was restored in µmt mice by infusing normal plasma, consistent with opsonization of endogenous TLR7 ligands by immunoglobulin. Although autoantibody production and glomerulonephritis are abolished in interferon receptor $(IFNAR)^{-/-}$ mice, both wild-type and $IFNAR^{-/-}$ mice developed anemia and BM hypocellularity following pristane treatment. These manifestations were absent in $TLR7^{-/-}$ and $TNF\alpha^{-/-}$ mice, indicating that the anemia is TNFα mediated. Unexpectedly, although TNF inhibitors can induce lupus manifestations, $TNF\alpha^{-/-}$ mice did not develop autoantibodies spontaneously. However, although IFN-I levels were comparable in untreated $TNF\alpha^{-/-}$ and B6 mice, $TNF\alpha^{-/-}$ mice had increased circulating pDCs and "pDC-like" cells, enhancing their potential to make IFN-I. When treated with pristane, $TNF\alpha^{-/-}$ mice developed more severe lupus than controls with increased levels of anti-Sm/RNP autoantibodies, IFN-I, pDCs, and peritoneal inflammatory ($Ly6C^{hi}$) monocytes.

Conclusions: Although autoantibodies and glomerulonephritis are TLR7/IFN-I dependent, lupus-associated BM abnormalities were TLR7/TNFα driven, but IFN-I independent. TNFα had a downregulatory effect on pDC numbers and TNFα-deficient mice exhibited an enhanced potential to produce IFN-I in response to TLR7 ligands. Our data suggest that the clinical manifestations of lupus reflect the complex interplay of cells producing IFN-I (causing autoantibodies and nephritis) and TNFα (causing hematologic involvement and arthritis). Engagement of TLR7 by RNA ligands released by dead cells may be a central defect in lupus, whereas the balance of IFN-I versus TNFα production may help determine the disease phenotype.

A28

Interferon-alpha and angiogenic dysregulation in pregnant lupus patients destined for preeclampsia

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Background: Pregnant patients with SLE are at increased risk of placental insufficiency and preeclampsia, disorders associated with angiogenic factor imbalance. IFNα, a critical element in SLE pathogenesis, is a potent antiangiogenic factor. In a case-control longitudinal study of lupus pregnancies from PROMISSE (Predictors of Pregnancy Outcome: Biomarkers In Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus), we investigated whether elevated IFNα early in pregnancy might be associated with poor pregnancy outcomes.

Methods: Each of 28 SLE patients with poor pregnancy outcome was matched to an SLE patient with an uncomplicated pregnancy and to a pregnant healthy control. Serum samples obtained monthly through pregnancy were assayed for IFNα activity using a reporter cell assay, and for antiangiogenic factor, sFlt1, and proangiogenic factor, placenta growth factor (PlGF). Human umbilical vein endothelial cells (HUVEC) were cultured in the presence of IFNα and/or sFlt1, and gene expression assessed by q-RT PCR. The effect of IFNα and sFlt1 on endothelial-trophoblast interactions was assessed in an *in vitro* model of spiral artery transformation in which the capacity of human first trimester extravillous trophoblasts to stabilize endometrial endothelial cell tube structures is measured.

Results: Compared with SLE patients with uncomplicated pregnancies, those with preeclampsia had increased IFNα before clinical symptoms. Nonautoimmune patients destined for preeclampsia did not have increased IFNα. In SLE patients with low IFNα, marked angiogenic imbalance (higher sFlt1, lower PlGF and higher sFlt1/PLGF ratios) precedes maternal manifestations of preeclampsia, whereas in SLE with high IFNα, preeclampsia occurs without evidence of systemic angiogenic imbalance. To investigate this result, we treated HUVEC with exogenous sFlt1 and IFNα. Treatment with sFlt1 induced the expression of *sFlt1* mRNA, and IFNα dramatically amplified the endothelial response to sFlt1, leading to a local positive feedback loop. Furthermore, in an *in vitro* model of spiral artery transformation, only IFNα and sFlt1 together disrupted the ability of trophoblast cells to remodel endothelial tube structures.

Conclusions: Our studies identify a new mechanism by which IFNα induces an antiangiogenic milieu in the vasculature leading to inadequate spiral artery remodeling and poor placentation early in pregnancy and maternal endothelial dysfunction presenting as preeclampsia later in pregnancy. They suggest that elevated IFNα may contribute to the pathogenesis of preeclampsia in some pregnant women with SLE.

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A29

Protective natural autoantibodies and lupus pathogenesis

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Background: Antibodies produced by B lymphocytes provide key functions that help protect against pathogens while recent studies show there can also be roles in maintaining homeostasis. Substantial levels of spontaneously arising IgM antibodies recognize cross-reactive oxidation-associated

epitopes, such as phosphorylcholine (PC) on apoptotic cells. One class of these natural antibodies can enhance efficiency of apoptotic clearance by innate immune cells, and also suppress proinflammatory responses. *In vivo* administration can block the development of the inflammatory autoimmune disease and enhance survival of lupus-prone mice. These inhibitory responses are linked to anti-inflammatory signaling with nuclear localization of MAPK phosphatase-1, a factor known to also mediate glucocorticoid suppression of immune responses.

Methods: To investigate the relevance to clinical SLE disease we analyzed the relationships between NAb levels with lupus disease activity, tissue injury and cardiovascular (CV) effects in two independent lupus cohorts.

Results: In 120 SLE patients from the Hopkins cohort, levels of IgM anti-PC were significantly higher in patients with low disease activity and with less organ damage by SELENA SLEDAI, as well as by the physician's evaluation and the SLICC damage score. Importantly, IgM anti-PC levels were also significantly higher in patients without histories of clinical CV events (that is, MI, angina or stroke). In 105 SLE patients from the NYU cohort, we found that subclinical CV disease, as detected by carotid ultrasound, correlated with lower levels of IgM anti-PC ($P = 0.004$), and also lower ratios of IgM anti-PC/total IgM, compared with patients without plaque ($P = 0.02$). The IgM anti-PC/total IgM association remained significant after adjusting for age, cholesterol and hypertension. Adiponectin and sE-selectin were significantly elevated in patients with plaque, and statistical models showed that combining adiponectin, sE-selectin and IgM anti-PC/total IgM was better for predicting plaque than either test alone.

Conclusions: Our clinical surveys have contributed to emerging evidence that regulatory anti-PC antibodies may oppose the influence of pathogenic lupus autoantibody ICs. Our data suggest that levels of anti-PC IgM antibodies may serve as a surrogate biomarker for vascular damage associated with subclinical atherosclerosis, and could have clinical applicability for monitoring and predicting relative risk in SLE patients.

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A30

A serine/threonine phosphatase, PP2A, controls autoimmunity

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Although tyrosine phosphatases have been well documented to be involved in the control of the immune system, serine/threonine phosphatases have not been assigned a similar role. Studies in patients with systemic lupus erythematosus (SLE), however, revealed that the protein, mRNA and catalytic activity of a serine/threonine phosphatase A (PP2A) are increased in T cells.

More importantly, PP2A has a master role in the aberrant biochemistry of SLE T cells because it: dephosphorylates pCREB and deprives an enhancer from various genes; dephosphorylates Elf1 and accounts for decreased expression of CD3ς and increased expression of FcRγ; activates (dephosphorylates) SP1 and promotes the expression of SP1-dependent genes such as CREM; and suppresses the activity of DNMT1 and promotes gene demethylation.

Gene function studies have revealed that promoter and intronic SNPs, along with epigenetic modifications of the promoter region, account for the expression of increased amounts of PP2A in SLE patients.

A mouse overexpressing PP2Ac in T cells does not develop autoimmunity but it displays increased amounts of IL-17 in the blood and develops florid glomerulonephritis when challenged with an anti-GBM antibody. Lastly, PP2A is involved in the epigenetic control of expression of IL-17.

Besides the increased expression of the catalytic subunit of PP2A, several regulatory (B) subunits appear to be abnormally expressed in SLE patients. Specifically, Bb' is decreased in one-half of SLE patients and accounts for defective IL-2 deprivation T-cell death, thus prolonging the survival of autoreactive T cells.

In conclusion, the catalytic and regulatory subunits of PP2A are abnormally expressed in SLE and contribute to aberrant T-cell function and organ damage. The fact that PP2Ac controls several downstream events urges its therapeutic targeting. The findings that PP2A B subunits control distinct T-cell function will enable corrective actions without the fear of collateral damage.

A31

The opportunity and imperative for point-of-care diagnostics in systemic lupus erythematosus

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Background: The development of point-of-care diagnostics (POCD) is prompted by the global burden of diseases attended by high morbidity and mortality when the diagnosis is delayed. POCD are designed to bring diagnostic tests immediately accessible to the site of patient care. In general terms, these devices are simple to use, economical, have high specificity and have a short turnaround time, enabling rapid clinical decisions. Contemporary POCD devices target blood glucose, coagulation, cardiac markers, infectious diseases, pregnancy and cholesterol testing. Systemic lupus erythematosus (SLE) is a suitable target for POCD because it can present with a variety of rapid-onset and life-threatening features, and is characterized by a number of well-defined disease-specific biomarkers. Clinical scenarios where POCD would benefit the management of SLE include CNS lupus (psychosis, encephalitis, stroke, seizures), transverse myelitis, acute renal failure, pulmonary hemorrhage and pneumonitis, cytopenias (thrombocytopenia, anemia, neutropenia, leukopenia), catastrophic antiphospholipid syndrome, cardiac tamponade and infarction, fetal heart block, mesenteric vasculitis and pancreatitis.

Methods: In collaboration with Dr Fooke Laboratorien GmbH (Neuss, Germany) we are developing and beta testing a lateral flow POCD that detects anti-dsDNA within 20 minutes after application of 10 µl serum. Twenty preselected SLE sera and age and gender-matched controls were tested. Interpretation of the test results were performed by direct visual observation or by densitometry using a portable lateral flow assay reader. Semi-quantitative results were expressed as relative units.

Results: When compared with results of the conventional *Crithidia lucilliae* assay, the POCD had a sensitivity of 90% and a specificity of 100%. Further testing to establish sensitivity, specificity and receiver operator characteristic in unselected SLE and control sera are underway.

Conclusions: Pilot data using this lateral flow POCD were favorable and had similar characteristics as those recently published by N Offermann in the *Journal of Immunological Methods*. The features of future POCD are based on advanced diagnostic platforms such as lateral flow, novel nanomaterials and microfluidics (lab on a chip), which are miniaturized and portable, have high specificity and design, are multiplexed and high throughput, and are standardized.

A32

Molecular characterization of proliferative lupus nephritis

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Background: The molecular events occurring within the kidney at diagnosis of lupus nephritis (LN) are incompletely understood. Despite use of intense immunosuppression, response rates are disappointingly low. We postulate that characterizing these events will lead to biomarker discovery and guide therapeutics. As proof of concept we evaluated the molecular pathology of LN kidney biopsies in a Latino cohort.

Methods: We studied 19 pairs of proliferative LN biopsies and four normal control biopsies using Nanostring RNA technology. All patients had at least two biopsies with the first at LN flare and the second after a median follow-up of 8 months. Based on clinical parameters, five patients achieved complete remission (CR), 10 partial remission (PR) and four had no response (NR) by the time of repeat biopsy. A panel of 511 immune-response genes was analyzed for each biopsy. Data were $\log_2$ transformed and quartile normalization was used to normalize data across samples. A linear model was used to compare the four groups (normal/CR/PR/NR) at baseline and a paired *t* test was used to compare baseline expression data at baseline and follow-up for each patient.

Transcripts were considered to be differentially expressed if they differed by at least twofold and if $P < 0.01$.

Results: At flare, three transcripts were uniquely expressed in CR, seven transcripts in PR, and 20 transcripts in NR when compared with normal. When compared with NR flares, CR flares showed increased MME, FADD, and CD274 and decreased ITGB2 and C1S expression. Change in transcript expression from initial to repeat biopsy was compared within each group and between groups. From biopsy 1 to biopsy 2, the CR group showed increased NCAM1 and decreased ILRL1 and FKBP5 expression. The NR group showed increased IL1RAP and CD5 and decreased C7, IL28B, and IL12RB1 expression. When compared with the CR group, the NR group showed increased IL17a, NOS2, FCAR and IL1RAP and decreased NCAM1, C7, and IL28B expression. NR flares had significant activation of T-cell and B-cell receptor signaling, IL-10, STAT3, and TNF-R pathways when compared with CR flares. Compared with NR flares, CR flares showed significant activation of T-cell regulation, antigen presentation, and apoptotic pathways.

Conclusion: The results of this study suggest that the molecular characteristics of responders are different than nonresponders. These data imply that molecular analysis of LN biopsies may provide prognostic information and guide choice of therapy.

A33

Disease features and outcomes among US lupus patients of Hispanic origin and their Mestizo counterpart in Latina America

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Background: Systemic lupus erythematosus (SLE) US Hispanic patients with a large Amerindian ancestral background have been found to have poor outcomes. Similar observations have been made in the mixed population of Latin America. We are now comparing and contrasting selected sociodemographic and clinical features and outcomes of lupus patients from these two groups.

Methods: SLE US Hispanic patients (European and Amerindian ancestry) from the LUMINA cohort (Lupus in Minorities: Nature vs. Nurture) and Latin American Mestizo patients from the GLADEL cohort (Grupo LatinoAmericano De Estudio de Lupus (Latin American Group for the Study of Lupus)) constitute the study population. Only patients who fulfilled four of the 1997 ACR criteria were included. Diagnosis time was time to the fourth criterion. Demographic and clinical data from these patients were extracted. When the ascertainment method for a specific variable was different in both cohorts, this has been noted. All variables were then compared using descriptive statistical tests. Adjustment for disease duration was done when indicated using either a Poisson regression or logistic regression, as appropriate.

Results: Salient features for these two patient groups are presented in Table 1. Some of the differences observed in terms of the socioeconomic features could be due to the different methods of ascertainment.

Conclusions: Patients in both cohorts exhibited active disease, with renal involvement and damage being frequent, and overall damage accruing rapidly; however, the US Hispanic patients exhibited a higher mortality. These two patient groups were also of low SES. These data suggest that these two populations share an underlying genetic background which coupled with a poor SES places them at increased risk for severe lupus with unfavorable short, intermediate and long-term outcomes. The less favorable mortality experience of the US Hispanics deserves to be further examined.

Acknowledgements: Thanks to LUMINA and GLADEL investigators on whose behalf this work is being presented.

A34

Elevated risk of chronic obstructive pulmonary disease in systemic lupus erythematosus: a population-based study

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Background: Chronic obstructive pulmonary disease (COPD) has been recently recognized as an inflammatory disease. A recent Swedish hospital-based study found an increased risk of COPD in patients with a number of autoimmune conditions including systemic lupus erythematosus (SLE). We wonder whether the risk is also present in SLE patients from the general population. The objective was to assess the future risk of newly recorded COPD cases among incident SLE cases compared with controls from the general population using physician billing and hospitalization data that cover the entire province of British Columbia (BC), Canada.

Methods: Our data include all health professionals and hospital visits covered by the comprehensive provincial medical services plan (1990 to 2010) and all dispensed medication (1996 to 2010), for all BC residents. We conducted a retrospective matched cohort (1996 to 2010) study

Table 1(abstract A33) Salient features of US Hispanic SLE patients from LUMINA and Latin America Mestizo patients from GLADEL (at diagnosis or at last visit)

Characteristic	LUMINA (n = 114)	GLADEL (n = 619)	P value
Age, mean (SD)	31.3 (12.2)	29.4 (12.6)	0.138
Gender (female), *n* (%)	106 (93.0)	546 (88.2)	0.135
Disease duration (years), mean (SD)	6.1 (4.3)	4.5 (4.6)	<0.001
Low SES[a], *n* (%)	42/107 (39.3)	391 (63.2)	<0.001
Health insurance, *n* (%)	56/112 (50.0)	466/615 (72.5)	<0.001
Acute onset, *n* (%)	34 (29.8)	151 (24.4)	0.220
ACR criteria number[b], mean (SD)	6.8 (1.6)	6.3 (1.5)	0.069
Disease activity (moderate-high)[c], *n* (%)	78/92 (84.8)	438/493 (88.8)	0.268
Renal disorder, *n* (%)	60 (52.6)	370 (59.8)	0.155
SDI score at last visit[b], mean (SD)	2.3 (2.6)	1.7 (1.7)	<0.001
Renal damage (per SDI, at last visit)[d], *n* (%)	37 (32.5)	184 (29.7)	0.559
Deceased[d], *n* (%)	21 (18.4)	35 (5.7)	<0.001

SES, socioeconomic status; ACR, American College of Rheumatology; SDI, SLICC (Systemic Lupus International Collaborating Clinics) Damage Index. [a]SES defined as being below the Federally-defined poverty line for LUMINA and as per the Graffar method for GLADEL. [b]After adjusting for disease duration in a Poisson regression model. [c]Defined as a SLAM (Systemic Lupus Activity Measure) >7 for LUMINA and a SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) >4 for GLADEL. [d]Significant after adjusting for disease duration using a Poisson regression model (for the SDI) and logistic regression for mortality

Table 1(abstract A34) Risk of incident COPD according to SLE status

	SLE (*n* = 4,486)	Non-SLE (*n* = 47,190)
COPD cases, *n*	96	419
Incidence rate/1,000 person-years	5.0	2.1
Age-matched, sex-matched, and entry time-matched RRs (95% CI)	2.3 (1.8 to 2.9)	1.0
<1 year of disease duration	6.1 (4.0 to 9.2)	1.0
1to 4.9 years of disease duration	1.7 (1.2 to 2.5)	1.0
5+ years of disease duration	1.5 (0.9 to 2.3)	1.0
Multivariable RR (95% CI)	2.0 (1.5 to 2.6)	1.0

among patients satisfying at least one of the following validated criteria: one diagnostic code for SLE (ICD-9-CM = 710.0) on at least two visits within a 2-year period by a nonrheumatologist physician; one ICD-9 code by a rheumatologist or from hospitalization; and absence of a prior SLE diagnosis between 1990 and 1995. Ten controls matched by birth year, sex and calendar year of exposure were randomly selected from the general population for each case. Outcome: we used a validated criteria to define COPD (first ICD-9-CM: 491, 492, 496, 493.2, or ICD-10-CM J43 or J44) from hospitals or death certificates. We estimated relative risks (RRs) by comparing SLE cases with age-matched, sex-matched and entry-time-matched comparison cohorts, adjusting for confounders. Sensitivity analyses were conducted to assess for unmeasured confounders.

Results: Among 4,486 individuals with incident SLE, 96 developed COPD (incidence rate = 4.96 per 1,000 person-years) (Table 1). The age-matched, sex-matched and entry-time matched RRs were significantly increased in the SLE cohort when compared with controls (RR 2.31, 95% CI 1.83 to 2.89). After adjusting for covariates the results remained statistically significant. The risk of developing COPD was highest within the first year following the diagnosis of SLE, decreasing over time and remaining significant up to 4 years after diagnosis. Our results remained statistically significant after adjusting for the potential impact of an unmeasured confounder (adjusted RRs ranging between 1.58 and 1.98 in all sensitivity analyses).

Conclusions: This is the first general population-based study indicating a twofold increased risk of COPD in patients with SLE. The risk of developing COPD was highest within the first year, declining thereafter, suggesting the potential pathogenic role of inflammation in the development of COPD.

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A35

Cancer risk factors in systemic lupus erythematosus: multivariate regression analysis in 16,409 patients

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Background: Patients with systemic lupus erythematosus (SLE) experience an increased risk of cancer, which is particularly driven by hematological malignancies. Our objective was to determine whether certain factors (demographics, SLE duration and calendar year) were associated with cancer risk in SLE, relative to the general population, using a large multicenter clinical cohort.

Methods: We present detailed analyses of a multisite international SLE cohort (30 centers, 16,409 patients). Cancers were ascertained by registry linkage. Standardized incidence ratios (SIR; ratio of observed to expected cancers) were calculated for overall and for hematological cancer risk, representing the relative risk of cancer for SLE patients, versus the age, sex, and calendar-year-matched general. We used Poisson hierarchical regression to assess for potential independent effects of the factors examined (sex, race/ethnicity, age group, SLE duration, calendar-year period) on the SIRs

Table 1(abstract A35) Results of adjusted multivariate regression to determine independent effect of variables on SIR* estimates for cancer in SLE

	Adjusted effects[a]	95% confidence interval
Female sex	1.00	0.77 to 1.30
Race/ethnicity		
White	Reference group	
Black	0.75	0.58 to 0.97
Asian	1.18	0.85 to 1.62
Age		
<40	Reference group	
40 to 59	0.72	0.55 to 0.94
60+	0.55	0.42 to 0.73
SLE duration		
<5 years	Reference group	
≥5 years	0.74	0.61 to 0.89
Calendar-year period		
<2000	Reference group	
≥2000	0.95	0.79 to 1.15

[a]Variables adjusted concomitantly for all others (sex, race/ethnicity, age, SLE duration, calendar-year period).

among the SLE cohort members. The hierarchical nature of the model allowed for differences in effects from one country to the next.
Results: In adjusted analyses (Table 1), we demonstrated lower SIR estimates for overall cancer risk, in black versus white SLE patients, in SLE patients of older versus younger age, and for patients with SLE duration of 5 years or more (versus lower duration). Female sex and calendar year were not clearly associated with any differences in the SIR estimates for SLE patients. Regarding hematological cancer specifically, SLE duration of 5 years or more again appeared to be associated with lower SIR estimates.
Conclusions: Although cancer risk in SLE is increased relative to the general population, patients most at risk appear to be those of white race/ethnicity, younger age, and of shorter SLE duration.

A36

Serological features of systemic lupus erythematosus diagnosed after referral through a rheumatology triage system because of positive antinuclear antibodies

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Background: The initial diagnosis of systemic lupus erythematosus (SLE) is made in a number of clinical settings, which include referrals to a specialist because of a constellation of symptoms and/or abnormal laboratory findings. Although a positive antinuclear antibody (ANA) test has been regarded a serological hallmark of SLE, it is also associated with a number of other systemic autoimmune rheumatic diseases (SARD). We studied the serological features of patients who were referred through a central triage (CT) system because of positive ANA and were then diagnosed as having SLE by the consulting rheumatologist.
Methods: Patients who met four criteria were included in the SLE cohort: referred to CT over 3 years; reason for referral was positive ANA; evaluated by a certified rheumatologist; and diagnosed as SLE. Clinical information from the first rheumatologic visit was extracted from the consultant's report. An anonymous CT database was developed to contain clinical information and an anonymous serological database was used for autoantibody test results.
Results: A total of 15,357 patients were referred through the CT; 643 (4.1%) because of positive ANA and, of these 263 (40.9%) were evaluated by a rheumatologist. In 24/263 (9.1%) ANA-positive patients, the rheumatologist provided a diagnosis of SLE, while 39 (14.8%) had a diagnosis of another autoantibody-related rheumatic disease (AARD), 69 (26.2%) had no evidence of any disease, 29 (11%) had conditions that did not meet classification criteria for an AARD and the remainder (102, 38.8%) had a variety of rheumatologic diagnoses. The age range of the SLE patients was 25 to 73 years (mean 44.4 years), 95.8% were female, 87.5% were referred by a family physician and the average waiting time was 137.3 days. The serological profile of the 24 SLE patients included 29.1% anti-Sm, 25% anti-U1RNP, 25% anti-ribosomal P, 25% anti-SS-A/Ro60, 25% anti-Ro52/TRIM21, 8.3% anti-dsDNA but none were anti-DFS70-positive.
Conclusions: This is the first study to evaluate the serological features of patients who were diagnosed on their first visit as having SLE after they were referred through a CT system because of positive ANA. Approximately 10% of the ANA referral patients were diagnosed as SLE and anti-Sm was the most common (~29%) autoantibody detected. This study provides an assessment of patients referred for positive ANA and implies that serological parameters might be helpful in determining the level of urgency of the referral.

A37

Sociodemographics and epidemiology of serious infections requiring hospitalization among adults with systemic lupus erythematosus and lupus nephritis, 2000 to 2006

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Background: Serious infections are among the leading causes of hospitalization, morbidity, and mortality in systemic lupus erythematosus (SLE) patients. Patients with lupus nephritis (LN) may be especially vulnerable. We investigated the sociodemographics and epidemiology of serious infections requiring hospitalization in a nationwide cohort of SLE and LN patients enrolled in Medicaid, the US federal-state insurance for low-income individuals.
Methods: We used the Medicaid Analytic eXtract (MAX) data system, with billing claims and demographics for >24 million Medicaid enrollees from 47 states and Washington, DC, 2000 to 2006. We identified patients aged 18 to 65 years with prevalent SLE (≥3 visits ≥30 days apart with ICD-9 codes of 710.0) and prevalent LN (≥ICD-9 codes for nephritis, proteinuria and/or renal failure on or after SLE diagnosis, ≥30 days apart). We defined serious bacterial, viral, fungal and mycobacterial infections resulting in hospitalization using a validated administrative database method. We stratified infection prevalence in SLE and LN by subtype, sociodemographic factors (age, sex, race/ethnicity, region, socioeconomic status (SES)), and by a validated SLE comorbidity index. We used Poisson regression to calculate incidence rates (cases/person-years) of first and overall infection, stratified by age, sex and race/ethnicity.

Table 1(abstract A37) Serious infections requiring hospitalization in SLE and LN patients, stratified by sociodemographic factors and the SLE comorbidity index

	Prevalent SLE cohort (*n* = 43,274)	Prevalent LN cohort (*n* = 8,096)
Total number of patients with a serious infection, *n* (%)	7,823 (18.1)	3,035 (37.5)
Total number of episodes of serious infections	17,055	7,486
Age, *n* (%)		
18 to 34	2,738 (35)	1,489 (49.1)
35 to 50	3,385 (43.3)	1,063 (35)
51 to 65	1,700 (21.7)	483 (15.9)
Sex, *n* (%)		
Female	7,211 (92.2)	2,684 (88.4)
Male	612 (7.8)	351 (11.6)
Race/ethnicity, *n* (%)		
White	2,613 (33.4)	674 (22.2)
African American	3,465 (44.3)	1,568 (51.7)
Hispanic	915 (11.7)	429 (14.1)
Asian	272 (3.5)	148 (4.9)
Native American	141 (1.8)	59 (5.2)
Other	417 (5.3)	157 (5.2)
Region		
Northeast	1,502 (19.2)	578 (19.0)
South	3,187 (40.7)	1,198 (39.5)
Midwest	1,736 (22.2)	748 (24.7)
West	1,398 (17.9)	511 (16.8)
SES tertile		
SES 1 (lowest)	2,525 (32.3)	937 (30.9)
SES 2	2,402 (30.7)	1,001 (33.0)
SES 3 (highest)	2,441 (31.2)	935 (30.8)
SLE specific risk index[a]		
Index 1 (lowest)	2,298 (29.4)	1,164 (38.4)
Index 2	3,478 (44.5)	864 (28.5)
Index 3 (highest)	2,047 (26.2)	1,007 (33.2)

[a]SLE-specific modification of the Charlson comorbidity index developed by MM Ward and more predictive of in-hospital mortality than the Charlson index among SLE patients.

Results: We identified 43,274 patients with SLE and 8,096 with LN. Mean age was 38 (SD 12) for SLE and 34 (SD 12) for LN. In the SLE cohort, 93% were female, 38% were Black, 37% White and 15% Hispanic; and in the LN cohort, 89% were female, 48% were Black, 23% White, and 17% Hispanic. We identified 17,055 episodes of serious infections requiring hospitalization in 7,823 SLE patients (28%) and 7,486 episodes in 3,035 LN patients (38%). Among SLE patients, the highest percentages of infections occurred in 35 to 50 year olds, in females, African Americans, in the South and in the lowest SES group (Table 1). The incidence rates of serious infection per 100 person-years were 15.4 for SLE and 34.5 for LN. In both cohorts, the majority (98%) of infections were bacterial - pneumonia and bacteremia; the most common viral infections were herpes zoster and influenza.
Conclusions: In this diverse, nationwide cohort of SLE and LN patients, we observed a significant burden of serious infections requiring hospitalization, most pronounced in LN patients. Further research is necessary to examine risk factors, particularly medication use, by sociodemographic groups.

A38

Preliminary population-based incidence and prevalence estimates of systemic lupus erythematosus: the California Lupus Surveillance Project

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Background: Previous estimates of prevalence and incidence of systemic lupus erythematosus (SLE) in the United States have varied widely due to factors such as heterogeneous source populations, limitations with case ascertainment, and differing case definitions. The California Lupus Surveillance Project (CLSP) is part of a national effort funded by the Centers for Disease Control and Prevention to determine more credible estimates of incidence and prevalence of SLE, with a special focus on Hispanics and Asians.
Methods: The CLSP is a population-based registry designed to determine the incidence and prevalence of SLE in San Francisco County, CA, USA. Sources of cases included hospitals, rheumatologists, nephrologists, commercial laboratories, and state population databases. These sources were queried for the International Classification of Diseases, Ninth Revision (ICD-9-CM) codes of 710.0 (SLE), 695.4 (discoid lupus), 710.8 (other specified connective tissue disease), and 710.9 (unspecified connective tissue disease). Laboratories were queried for serologic tests including ANA, anti-dsDNA, anti-Smith, antiphospholipid antibodies, and low complement levels. Pathology laboratories were queried for renal and cutaneous biopsies consistent with lupus. Over 15,000 potential SLE patients were identified after the initial queries, and trained abstractors performed detailed medical chart reviews on the >5,500 patients who met the catchment criteria of residence in San Francisco County within the years 2007 to 2009. Cases were defined as patients with documentation of ≥4/11 of the ACR Classification Criteria for SLE. Using SAS 9.3, we calculated prevalence and incidence rates and associated 95% confidence intervals (CIs). Denominators for all rates were obtained from the US Census data (revised 2000 to 2009 intercensal population files) for San Francisco County.
Results: The preliminary overall crude prevalence and incidence of SLE in San Francisco County was 90.4/100,000 and 5.1/100,000 respectively. The highest prevalence of disease was observed in Black women (430.6/100,000), followed by Hispanic and Asian (163.8/100,000 and 158.9/100,000, respectively), and White (111.3/100,000) women (Table 1).
Conclusions: The CLSP uses more complete case finding methods to provide current estimates of prevalence and incidence in a racially and ethnically diverse population. Racial and ethnic disparities in SLE were confirmed with the highest burden of disease in Black women, followed by Hispanic and Asians, and, finally, White women.

A39

Serious infection incidence rates in pediatric systemic lupus erythematosus according to medication use

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Background: We investigated incidence rates of serious infections among children with systemic lupus erythematosus (SLE) and lupus nephritis (LN) enrolled in Medicaid, the US health insurance program for low-income children and parents.
Methods: We identified all children aged 5 to <18 years with SLE (≥3 ICD-9 codes of 710.0, each >30 days apart) and LN (≥2 ICD-9 codes for renal disease on/after SLE diagnosis) in the Medicaid Analytic eXtract (MAX) from 2000 to 2006. This dataset contains all outpatient and inpatient Medicaid claims for enrollees in 47 US states and the District of Columbia. Filled prescriptions were documented and patients were classified as new users of

Table 1(abstract A38) Preliminary prevalence and incidence rates (per 100,000) of SLE in San Francisco County, CA, USA

	Prevalence (2007)		Incidence (2007 to 2009)	
Race/ethnicity, sex	Number of cases	Crude rate (95% CI)	Number of cases	Crude rate (95% CI)
Overall	704	90.4 (84.0 to 97.3)	121	5.1 (4.3 to 6.1)
Women	623	162.0 (149.8 to 175.2)	112	9.6 (8.0 to 11.5)
Men	81	20.6 (16.5 to 25.5)	9	0.7 (0.4 to 1.4)
Black	138	243.0 (205.7 to 287.0)	27	15.9 (10.9 to 23.1)
Women	121	430.6 (360.5 to 514.2)	25	29.9 (20.3 to 44.2)
Men	17	59.2 (37.0 to 94.9)	2	2.3 (0.6 to 8.4)
White	255	58.1 (51.4 to 65.7)	43	3.2 (2.4 to 4.3)
Women	230	111.3 (97.8 to 126.6)	38	6.0 (4.4 to 8.3)
Men	25	10.8 (7.3 to 15.9)	5	0.7 (0.3 to 1.7)
Asian	264	95.8 (84.9 to 108.1)	39	4.6 (3.4 to 6.3)
Women	233	158.9 (139.8 to 180.7)	37	8.3 (6.0 to 11.4)
Men	31	24.0 (16.9 to 34.1)	2	0.5 (0.1 to 1.9)
Hispanic	99	87.7 (72.1 to 106.8)	17	4.9 (3.1 to 7.8)
Women	87	163.8 (132.9 to 202.0)	16	9.8 (6.0 to 15.9)
Men	12	20.1 (11.5 to 35.1)	1	0.5 (0.1 to 3.1)

Table 1(abstract A39)

	Systemic lupus erythematosus		Lupus nephritis	
	Unadjusted IRR (95%CI)	**MV-adjusted[a] IRR (95% CI)**	**Unadjusted IRR (95%CI)**	**MV-adjusted[a] IRR (95% CI)**
HCQ	Reference	Reference	Reference	Reference
CS	**5.25 (4.07, 6.78)**	**3.58 (2.79, 4.59)**	**2.13 (1.51, 3.01)**	**1.90 (1.36, 2.67)**
IS	**2.58 (1.86, 3.58)**	**2.46 (1.80, 3.37)**	1.28 (0.80, 2.05)	1.12 (0.70, 1.78)
CS+IS	**2.90 (2.03, 4.14)**	**1.99 (1.41, 2.80)**	NR	NR

NR, not reported in accordance with CMS policy. [a]Multivariable adjusted models included age, sex, race/ethnicity, US residential region, area-level SES, SLE severity index.

hydroxychloroquine (HCQ), corticosteroids (CS) and immunosuppressants (IS). We identified serious infections from hospital discharge diagnosis codes for all infections, and for specific subtypes of infections (bacterial, fungal and viral). We calculated incidence rates per 100 person-years (PY) overall and by medication subgroup. Incidence rate ratios (IRR) (95% CI) were calculated comparing CS, IS and CS+IS with HCQ alone using Poisson models, adjusted for age, sex and duration of enrollment in Medicaid.
Results: Among the 2,403 children with SLE who were new medication users, there were 316 serious infections in 2,215 PY. Incidence rates for all serious infections requiring hospitalization varied between 10/100 PY for SLE and 25.7/100 PY for LN. Among children with SLE receiving CS alone, incidence rates of serious infections were 3.5 times higher compared with those not receiving CS or IS. Among children receiving both CS and IS, overall serious infection incidence rates were twice as high compared with children not receiving either medication (Table 1).
Conclusions: Infection remains a common complication of SLE and is associated with significant morbidity and mortality. We observed high rates of serious infections requiring hospitalization among children with SLE and LN. Those children receiving CS alone or in combination with IS had much higher rates of serious infections, compared with those children receiving HCQ alone.

A40

Smoking and secondhand smoke among patients with systemic lupus erythematosus and controls: associations with disease and disease damage

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Background: Previous reports suggest smoking may be a risk factor for developing systemic lupus erythematosus (SLE). This study explores the impact of tobacco smoke on SLE patients compared with controls and on disease characteristics among patients.
Methods: Data from a cohort of SLE patients and controls were utilized. Medical history, smoking and secondhand smoke exposure history, SLE Disease Activity Index (SLEDAI) and SLICC Damage Index (SDI) scores were collected at an in-person enrollment visit and confirmed by chart review. Statistical analysis used chi-square testing and multivariate logistic regression.
Results: There were 545 SLE patients and 386 controls with data available for analysis (Table 1). At enrollment, the mean age was 37.6 ± 14.7 years for patients and 42.0 ± 15.4 years for controls. Differences between current and never smokers ($P = 0.51$) and ever and never smokers ($P = 0.70$) were not significantly different between patients and controls. Compared with unrelated controls, African American patients were significantly more likely to be exposed in the home to secondhand smoke before the age of 18 (OR 1.81, 95% CI 1.13 to 2.89). Damage by SDI (SDI > 0) was significantly associated with ever smoking (OR 3.08, 95% CI 1.4 to 6.6), current smoking (OR 3.17, 95% CI 1.1 to 9.1), and secondhand smoke exposure in childhood (OR 1.91, 95% CI 1.0 to 3.6). No significant relationship was found between smoking status and active disease at enrollment (SLEDAI ≥ 6) or dsDNA autoantibodies. Discoid rash was significantly associated with ever smoking (OR 2.74, 95% CI 1.5 to 5.1) and current smoking (OR 4.85, 95% CI 2.2 to 10.5).
Conclusions: Our study suggests that secondhand smoke during childhood may be a risk factor for SLE. Secondhand smoke during childhood, current smoking and past smoking contribute significantly to disease damage among patients with SLE.

A41

High mortality in North American Natives with systemic lupus erythematosus

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Background: Lupus outcomes including mortality have been found to be worse in most ethnic minorities, but little is known about North American Indigenous people (NAI). We compared mortality in NAI systemic lupus erythematosus (SLE) patients with Caucasian and other ethnic minority (OEM) SLE patients at a single academic center.
Methods: Patients were followed from 1990 to 2013 using a custom database. Variables included date of birth, diagnosis, year of disease onset, ethnicity, clinic visit dates, and vital status if known. Records of all patients with a diagnosis of SLE (≥4 American College of Rheumatology criteria) were abstracted. For patients who had not been seen in the last 2 years,

Table 1(abstract A40)

	Never smokers, *n* (%)	**Ever smokers, *n*** (%)	**Current smokers, *n*** (%)	**Secondhand smoke < 18 years old, *n*** (%)	**Secondhand smoke ever, *n*** (%)
All patients ($n = 545$)	407 (74.7%)	138 (25.3%)	72 (15.1%)	132 of 372 (35.5%)	158 of 376 (42.0%)
African American patients ($n = 416$)	328 (78.9%)	88 (21.2%)	49 (11.8%)	111 of 313 (35.5%)	127 of 315 (40.3%)
Caucasian patients ($n = 109$)	63 (57.8%)	46 (42.2 %)	21 (19.3%)	19 of 47 (40.4%)	26 of 47 (55.3%)
Other patients ($n = 20$)	16 (80%)	4 (20.0%)	2 (10%)	2 of 12 (16.7%)	5 of 14 (35.7%)
All controls (African American) ($n = 386$)	284 (73.6%)	102 (26.4%)	57 (14.8%)	92 of 354 (25.6%)	120 of 357 (33.6%)
Related controls ($n = 222$)	155 (69.8%)	67 (30.2%)	36 (16.2%)	51 of 205 (24.9%)	67 of 207 (32.4%)
Unrelated controls ($n = 164$)	129 (78.7%)	35 (21.3%)	21 (12.8%)	41 of 149 (27.5%)	53 of 150 (35.3%)

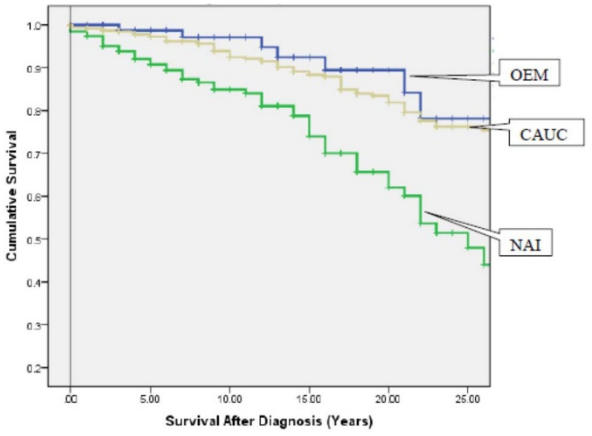

Figure 1(abstract A41) Kaplan-Meier survival curve.

updated vital status was obtained from the hospital medical records department. Ethnicity was by self-report, and categorized into NAI, Caucasian and OEM. The age at diagnosis, disease duration and age at last follow-up or age at death was calculated and compared between ethnic groups. Survival time was compared between ethnic groups using Kaplan-Meier and Cox proportional hazard models.

Results: A total of 807 patients with SLE were identified: 201 (25%) patients were NAI, 501 (62%) were Caucasian, and the remaining 105 (13%) were OEM. NAI and OEM patients were younger at diagnosis (NAI = 32 ± 15 years; OEM = 31 ± 14 years; Caucasian = 37 ± 15 years; $P = 0.001$), had a shorter disease duration (NAI = 11 ± 9 years; OEM = 10 ± 9 years; Caucasian = 15 ± 11 years; $P = 0.001$) and had more frequent nephritis (NAI = 41%; OEM = 49%; Caucasian = 29%; $P = 0.001$) compared with Caucasians. More NAI had died by the end of the follow-up period (NAI = 25%; OEM = 7%; Caucasian = 18%; $P < 0.001$) and mean age at death was much younger in both NAI and OEM (NAI = 50 ± 16 years; OEM = 46 ± 14 years; Caucasian = 63 ± 16 years; $P = 0.001$). Survival rates were significantly worse in NAI compared with OEM and Caucasians (Figure 1): 10-year survival 85% versus 97% and 92%; 15-year survival 75% versus 89% and 88% respectively ($P < 0.001$). In a Cox proportional hazards model, the risk of death following diagnosis was higher for NAI (hazard ratio 2.5; 95% CI: 1.6 to 3.9) after adjustment for onset age, damage, and lupus manifestations.

Conclusions: NAI and OEM patients had similarly young onset age and more frequent nephritis, but survival was markedly worse in NAI compared with Caucasians. Urgent improvements in care delivery for NAI with SLE are needed to decrease the significant morbidity and mortality burden from this disease.

A42

Optimal determination of Physician Global Assessment of lupus disease activity: a pilot study

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Background: The Physician Global Assessment (PGA) is an important and useful outcome measurement of lupus disease activity. Consensus on when the PGA should be performed is lacking; many lupus specialists determine the PGA at the time of a patient visit while others determine the PGA after receipt of laboratory values. The objective of this study was to collect preliminary data to determine the optimal time to perform a PGA.

Methods: In this pilot study, a PGA was performed by a single clinician upon completion of an outpatient clinical encounter and again after receipt of pertinent laboratory values. The pre-laboratory PGA was determined with knowledge of the subject's previous laboratory values and lupus history, while the post-laboratory PGA was determined after laboratory reports from the patient clinical encounter were also available. Disease activity could range from 0 to 3, with 0 representing no disease activity, 1 representing mild disease activity, 2 representing moderate disease activity and 3 representing the most severe lupus disease imaginable. Laboratory values obtained at each clinical visit included a CBC, comprehensive chemistries, C3, C4, anti-dsDNA, urinalysis and, if pertinent, a spot urinary protein/creatinine ratio. Disease duration and SELENA SLEDAI were recorded. Results are presented using descriptive statistics; the paired Student's *t* test was utilized to compare the pre-laboratory PGA with the post-laboratory PGA.

Results: Thirty-three patients, three male and 30 female with an average SLE disease duration of 12.3 (range 1 to 36) years, contributed 74 assessments to this study. The average SELENA SLEDAI was 2.21. The average pre-laboratory PGA was 0.45 and the average post-laboratory PGA was 0.55 ($P = 0.02$ paired Student's *t* test). Twenty-six pre-laboratory PGAs were evaluated as 0, 23 remained at 0 after receipt of laboratory examinations, and three increased secondary to new lupus serologic activity. The pre-laboratory and post-laboratory PGAs were equal in 17 of 53 encounters with disease activity (that is, PGA > 0). The average pre-laboratory PGA of these 53 encounters was 0.67, the average post-laboratory PGA was 0.77 ($P < 0.05$, paired Student's *t* test) and the average SELENA SLEDAI was 3.12 (range 0 to 8).

Conclusions: In some lupus patients, the PGA determined prior to receipt of laboratory values may be the same as the PGA determined after labs are received. However, in these preliminary data, there was a significant difference between pre-laboratory and post-laboratory PGA. Further studies in a larger patient population are needed to confirm and extend these findings.

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Outcome measures in systemic lupus erythematosus: constructing a meaningful response index from existing clinical trial data

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Background: The purpose of this project is to develop a systemic lupus erythematosus (SLE) response index as a standard outcome measure in future therapeutic trials. Currently, there is no widely validated method for defining response to therapy. Most SLE trials to date have failed to meet predesigned endpoints, leading to controversy over whether it is drug treatments or outcome measures that are unsuccessful in SLE. A similar controversy in rheumatoid arthritis (RA) years ago was resolved by examining data from placebo-controlled trials with drugs that were only modestly effective. Important clinical variables were selected, criteria for patient improvement determined, and an index was developed that distinguished treated patients from those getting placebo. This index (ACR 20/50/70) used in RA trials has led to approval of more than 20 drug therapies.

Methods: Now that large-scale SLE clinical trial data exist, we propose to use the approach that was successful in RA. We will perform a *post-hoc* analysis of the raw data from the BLISS-52 and BLISS-76 trials investigating belimumab for SLE. The disease activity indices (SELENA SLEDAI and BILAG) will be deconstructed and individual clinical and laboratory parameters will be identified (for example, rash, complement). The variables that are present in the majority of patients, improve over time, and have face validity will be selected for this index. Both the physician global assessment and a patient-related measure of quality of life will be included.

Results: Study data will be split 50/50 into a training set and a validation set. Baseline values of variables will be compared with values at the end of the study to determine the degree of improvement or deterioration occurring in individual patients during the study. We will examine various threshold percent-improvement cutoff points across sets of variables, selecting those that produce the largest difference between placebo-treated and drug-treated patients while retaining an acceptably low proportion of improved placebo-treated patients. We will follow the methodology outlined by Harold Paulus in previous work for RA. The index will be tested by applying it to the remaining set of study subjects (validation set) used to derive the criterion. Performance measures will include discriminative ability, calibration and overall accuracy.

Conclusions: This new composite index will be simple to use, based on real individual patient clinical trial data, and will include patient-reported outcome measures. The index should serve to prevent useful drugs from being discarded due to inadequate trial designs. Preliminary data will be presented.

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Significance of cerebrovascular reactivity in patients with systemic lupus erythematosus

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Background: There is growing recognition and concern regarding cognitive dysfunction in patients with systemic lupus erythematosus (SLE). SLE patients have accelerated atherosclerosis, which is known to contribute to cognitive dysfunction in other disease states. Impaired cerebrovascular reactivity (CVR) is a vascular measure linked to cognitive dysfunction, but this has not been well studied in the setting of SLE. The objectives of this study are to determine whether CVR is impaired in patients with SLE and to determine the significance of CVR impairment.
Methods: Right middle cerebral artery CVR was assessed by the breath holding index (BHI), which combines transcranial Doppler recording and passive breath holding. This technique evaluates changes in middle cerebral artery Doppler velocities upon permissive hypercapnea. We measured the BHI in nine female patients with SLE (age 38 ± 13 years) and 12 age-matched controls. Cognitive function was assessed using the color Stroop block time test (SBT) and the Stroop black/white test (SBWT). The augmentation index, a measure of arterial wave reflection, was assessed by applanation tonometry of the radial artery. Carotid intimal media thickness measurements were obtained with high-resolution ultrasound.
Results: Completion times for the SBT (38.4 ± 8.7 vs. 29.5 ± 6.6) and the SBWT (29.7 ± 5.4 vs. 22.9 ± 5.8) were significantly higher in SLE patients versus controls ($P = 0.005$ and $P = 0.004$ respectively). On CVR testing, right middle cerebral artery BHI responses were significantly different between SLE and NLS (0.91 ± 1.10 vs. -0.99 ± 1.7, $P = 0.001$). There was a trend towards higher CIMT (0.634 ± 0.130 cm vs. 0.549 ± 0.116 cm, $P = 0.10$) and towards higher AI (27 ± 16% vs. 18 ± 9%, $P = 0.10$) in the SLE group. CVR was significantly correlated with AI (0.68, $P = 0.003$), and a trend with SBT ($r = 0.42$, $P = 0.07$) and CIMT ($r = 0.45$, $P = 0.08$). On multivariate analysis (with age and SLE), SLE was a significant predictor of BHI ($B = 1.84$, $P = 0.033$).
Conclusions: SLE is associated with impaired CVR. Impaired CVR appears related to higher wave reflection as measured by the AI. This ongoing study will help define the relations between CVR and other vascular parameters as well as potential relations with cognitive dysfunction in SLE patients.

A45

'Lupus headache': results from a prospective, international, inception cohort study

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Background: 'Lupus headache' is controversial but included in measures of global SLE disease activity. We examined the frequency, characteristics and associations of 'lupus headache' in a large, prospective, inception cohort of SLE patients.
Methods: The study was conducted by an international network of 30 academic medical centers. Annual assessments were performed for 19 neuropsychiatric (NP) syndromes, which included five types of headache using the International Headache Society (IHS) criteria. Additional data were demographic and clinical variables, SLEDAI-2K, which includes 'lupus headache' as a standalone variable, SLICC/ACR damage index and self-report mental (MCS) and physical (PCS) component summary scores of the SF-36. Statistical analysis used linear regression models with generalized estimating equations.
Results: Of 1,732 enrolled patients, 89% were female. Race/ethnicity was Caucasian (48%), African (16%), Asian (16%), Hispanic (16%) and other (4%). At enrollment, the mean ± SD age was 34.6 ± 13.4 years, disease duration was 5.6 ± 4.8 months and follow up was 3.8 ± 3.1 years. Twenty-six (1.5%) patients had 'lupus headache' at 27 (0.36%) of 7,523 assessments with the following IHS classification: migraine ($n = 13$), tension headaches ($n = 8$), intractable nonspecific headaches ($n = 5$), cluster headaches ($n = 1$) and intracranial hypertension ($n = 1$). In 5/27 (18.5%) assessments there were concurrent NP events. 'Lupus headache' was reported at both enrollment ($n = 14$) and follow-up ($n = 13$) assessments, in patients from all racial/ethnic groups in 15 of 30 (50%) sites located in eight of 11 countries. The estimated mean (± SE) SLEDAI-2K scores, without the 'lupus headache' variable, for visits with no headache ($n = 6,019$), a nonlupus headache ($n = 1,330$) and both a nonlupus headache and 'lupus headache' ($n = 27$) were 3.8 ± 0.08, 3.6 ± 0.18 and 7.2 ± 1.40 respectively ($P = 0.034$). Concurrent SF-36 MCS scores were 47.8 ± 0.28, 42.6 ± 0.56 and 39.4 ± 2.41 ($P < 0.001$) and PCS scores were 42.6 ± 0.30, 38.1 ± 0.53 and 32.4 ± 1.76 ($P < 0.001$). SLEDAI-2K scores, without the 'lupus headache' variable, for patients with and without 'lupus headache' were 7.2 ± 1.40 versus 3.7 ± 0.08 ($P = 0.035$). In 5/26 (19.2%) patients, 'lupus headache' was the sole contributor to the SLEDAI-2K score. Concurrent SF-36 MCS and PCS scores for patients with and without 'lupus headache' were 39.4 ± 2.41 versus 46.8 ± 0.27 ($P = 0.002$) and 32.4 ± 1.76 versus 41.7 ± 0.28 ($P < 0.001$) respectively.
Conclusion: 'Lupus headache' was infrequent, associated with higher global disease activity and a lower HRQoL. It was not reproducibly aligned with a uniform IHS classification of headache (for example, intractable headache). The lack of consistency in diagnosing 'lupus headache', even by experienced clinicians, indicates a need to better define 'lupus headache' and to reach consensus on whether it is truly a standalone manifestation of NP SLE.

A46

Adverse pregnancy outcomes and subsequent risk of cardiovascular disease in women with systemic lupus erythematosus

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Background: Patients with systemic lupus erythematosus (SLE) are at increased risk for adverse pregnancy outcomes and cardiovascular disease (CVD). The objective of this exploratory study was to investigate the association between a history of adverse pregnancy outcomes and subsequent risk of subclinical CVD assessed by imaging studies and verified clinical CVD events in 129 women with SLE.
Methods: The occurrence of adverse pregnancy outcomes, specifically pre-eclampsia, preterm birth, and low birth weight, was ascertained by questionnaire. Subclinical CVD was assessed by coronary artery calcium (CAC) as measured by electron beam computed tomography (EBCT) and carotid plaque measured by B-mode ultrasound. Clinical CVD events were verified by medical record review. Logistic regression was used to estimate the association of pregnancy complications with occurrence of subclinical and clinical CVD with *a priori* adjustment for age, which is associated with CVD and SLE disease duration as a measure of SLE disease burden.
Results: Fifty-six women reported at least one pregnancy complication while 73 had none. Twenty-six women had at least one pregnancy complicated by pre-eclampsia and were more likely to have a CAC score ≥10 (adjusted odds ratio (OR) = 3.7; 95% confidence interval (CI): 1.2, 11.9), but the presence of plaque was not associated with this pregnancy complication (OR = 1.1; 95% CI: 0.4, 2.8). Low birth weight and preterm birth were not associated with CAC or plaque.
Conclusions: SLE patients with a history of pre-eclampsia had a higher rate of subclinical CVD as measured by CAC score. Future studies are needed to confirm the relationship between adverse pregnancy outcomes and subsequent subclinical CVD and clinical CVD events.

A47

Methodological quality of studies of end-stage renal disease risks in lupus nephritis

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Background: Variations in methodological quality can affect the results of individual studies and of systematic reviews. We examined the adequacy of patient descriptions, representativeness, and follow-up information in studies included in a systematic review of risks of end-stage renal disease (ESRD) in patients with lupus nephritis.
Methods: We search Medline, Embase, and the Cochrane Database from their inceptions to 31 December 2013 for studies that reported on ESRD in adults with lupus nephritis. We included all observational studies and long-term clinical trials with a minimum of 12 months of follow-up and 10 patients that reported specific data on the development of ESRD. Two authors independently assessed study quality using a modification of the Newcastle Ottawa scale, and rated studies on 10 items in three areas: adequacy of description of the cohort (items 1 to 3); representativeness (items 4 to 7); and adequacy of follow-up information (items 8 to 10).
Results: The literature search yielded 1,852 articles, of which 174 articles met our inclusion criteria. These included 132 observational studies and 42 clinical trials. The proportion of studies meeting each quality measure, stratified by study design, is presented in Table 1. Among observational studies, the median number of measures satisfied per study was 5 (range 2 to 9), and among clinical trials was 4 (range 2 to 7). There was no correlation between publication year and number of measures satisfied for observational studies ($r = 0.14$), but recent trials tended to satisfy more quality measures ($r = 0.32$; $P = 0.04$).
Conclusions: While both observational studies and clinical trials generally provided good clinical descriptions of the cohorts, few provided adequate data on follow-up. The representativeness of observational studies was low. The improvement in trial quality over time may be due to the development of standardized protocols and the institution of reporting standards, which might also serve to enhance the reporting of observational studies.
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A48

Patient-Centered Outcomes Research Institute (PCORI) multisite project to develop treatment decision aids for racial/ethnic minorities with lupus nephritis

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Background: The Patient-Centered Outcomes Research Institute (PCORI) was established to support research that informs US health reform. The PCORI aims to provide patients and the public with information to facilitate healthcare decision-making, including to 'develop, refine, test, and/or evaluate patient-centered approaches, including decision support tools.' Here we describe the first PCORI project in systemic lupus erythematosus (SLE), in which we aim to develop an individualized patient decision aid for lupus nephritis. The project uses a multiphase approach to develop and test a decision aid, combining comparative effectiveness research, qualitative research with patients, decision-aid prototype development, and a randomized controlled trial.
Methods: We performed comparative effectiveness research (CER) using state-of-the-art network meta-analyses to assess effectiveness and toxicities of treatments for lupus nephritis. Concurrently, patients with lupus nephritis participated in Nominal Group Technique (NGT) groups. Participants identified facilitators and barriers they faced when considering and taking drugs for lupus nephritis. In the coming year, information from the CER and NGT will be used to create a prototype decision aid, with input from diverse project stakeholders, including design consultants, clinicians, researchers, lupus organizations and patients. We will then perform a randomized controlled trial to assess the effectiveness of the decision aid (vs. usual care) in patients with incident or recurrent lupus nephritis. Primary outcomes include measures of decisional conflict and informed choice. Secondary outcomes include the control preferences scale and interpersonal processes of care, and exploratory outcomes will include medication adherence and persistence, cumulative glucocorticoid exposure, and renal response.
Results: The CER and NGT have been completed. Fifty-two patients, who were predominantly African American and Hispanic, participated in NGT groups. Patients identified barriers and facilitators to use of immunosuppressive drugs in two 1-hour sessions, each with three to nine patients. Data from CER and NGT are currently being analyzed. A prototype decision aid will be developed based on the results of the CER and NGT, and subsequently piloted in patients before the randomized trial.
Conclusions: The decision aid resulting from this project will be nonproprietary, free of cost and readily available for use both in the United States and internationally. Use of the tool is expected to facilitate patient-centered care for lupus nephritis by providing information that both scientific evidence and patients themselves indicate is critical before commencing therapy. The project aims to improve decision-making and health outcomes for lupus nephritis, particularly among racial/ethnic minorities.

A49

Clinical response to belimumab in academic clinical practices

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Table 1(abstract A47)

Quality measure	Observational studies (n = 132)	Clinical trials (n = 42)
1. ACR criteria for SLE used	88.3	88.1
2. Measure of renal function included	77.2	95.2
3. Treatments described	84.1	100
4. Community-based study	11.3	Not applicable
5. Inception cohort	40.1	11.9
6. Renal biopsy not required for inclusion	37.1	35.7
7. Patients with chronic kidney disease not excluded	80.3	23.8
8. Losses to follow-up described	24.2	42.8
9. Losses to follow-up < 20%	18.9	30.9
10. Data reported using Kaplan-Meier curves	36.3	9.5

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Background: Belimumab is a human monoclonal antibody that inhibits soluble B-lymphocyte stimulator and improves systemic lupus erythematosus (SLE) disease activity. This study was initiated to evaluate the use and efficacy of belimumab in academic SLE clinical practices.
Methods: An invitation to participate was sent to 16 physicians experienced in SLE phase III clinical trials. All agreeing to participate completed a one-page questionnaire for each patient prescribed belimumab that includes demographic and SLE characteristics, and information about belimumab administration. The questionnaire completed every 3 months by the physicians also captured clinical responses and belimumab safety. Clinical response was defined as a ≥50% improvement in the initial clinical manifestation being treated without worsening in other organ systems.
Results: Of 16 invitations sent, nine investigators participated. Questionnaires on 150 patients treated with belimumab for at least 3 months were available for analysis. The mean age was 41.9 ± 12.6 years. 92.0% were female, 67.1% White, 24.7% Black, 5.7% Asian, and 5.3% Hispanic. The average SLE disease duration was 12.2 ± 8.2 years. Concomitant medications included: prednisone in 73.3% (mean dose of 12.2 ± 10.9, 41.7% on ≥10 mg), antimalarials in 71.7%, and immunosuppressants in 66.3% (mycophenolate mofetil 34.2%, azathioprine 20.3%, methotrexate 11.8%). Only 3.7% of patients were not on any background SLE medications, 8.0% were on antimalarials alone. The dominant clinical manifestations driving treatment were arthritis in 69.5%, rash in 44.4%, and inability to taper steroids in 27.3%. Other SLE manifestations were serositis 16.0%, hematological 13.9%, and renal 10.7%. A total 65.2% of patients had ≥2 active manifestations. Of the 150 patients on belimumab for at least 3 months, 69 (46.0%) clinically responded by 3 months with marked improvement in arthritis and/or rash. Similarly, of the 112 patients on belimumab for at least 6 months for whom follow-up data were available, 54 (48.2%) clinically responded with improvements in arthritis, rash and/or nephritis. While the numbers are limited, black patients showed improvement at 6 months, with 19/26 (73%) of patients responding, $P = 0.05$.
Conclusions: These observational data support the use of belimumab across all racial/ethnic groups and efficacy similar to that reported in the phase III trials. Relevant to physician and patient decision-making, improvement was seen as early as 3 months.

A50

Eculizumab in recalcitrant antiphospholipid antibody syndrome

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Background: Antiphospholipid syndrome (APS) is defined as the occurrence of venous or arterial thrombosis and/or pregnancy morbidity, in the presence of serological evidence of antiphospholipid antibodies (including IgM and IgG anticardiolipin antibodies, IgM and IgG anti-β_2-glyoprotein I antibodies, or the lupus anticoagulant). Whereas most patients with focal thrombotic events respond to anticoagulation, occasional patients are refractory to standard therapeutic interventions and continue to have either focal or multifocal occlusive disease. For those with recalcitrant disease or those with the catastrophic antiphospholipid syndrome (CAPS), physicians resort to the addition of antiplatelet agents, steroids, immunosuppressives, IVIG, rituximab, or plasma exchange.
Complement inhibition may be an effective way to prevent thrombosis associated with APS. Eculizumab, a monoclonal antibody that binds to complement protein C5 and prevents the conversion of C5 to C5a and C5b, may potentially be an effective treatment for patients with APS. First studied in patients with systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, and idiopathic membranous nephropathy in the early 2000s, development of the drug for rheumatic diseases was abandoned in favor of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Given the experience of complement inhibition in animal models of APS as well as prior use of eculizumab several years ago in one of our refractory APS patients, we administered eculizumab to two patients with severe refractory APS.
Methods: Two patients with antiphospholipid syndrome, unresponsive to conventional anticoagulant therapy, were treated with a loading dose of eculizumab followed by dosing every other week (atypical hemolytic uremic syndrome dosing schedule). It has been suggested that the platelet count may be used as a surrogate marker of APS activity. During therapy, both patients' platelet counts were monitored and any new thrombotic events documented. At the time of submission of this abstract, both patients are continuing treatment with eculizumab.
Results: At their lowest values, the patients had platelet counts of 35,000 and 22,000 (K/ml). One of the patients was steroid dependent in order to maintain her platelet count. After initiation of eculizumab, the patient was able to taper steroids as the platelet count has risen from a low of 35,000 to average counts of 100,000. The second patient's platelet count rose to over 200,000 from 22,000 within 10 days of receipt of eculizumab. For both patients the increases in platelet counts have been sustained other than during brief periods when therapy was delayed. During the treatment period (4 and 8 months), there were no new thrombotic events. See Figure 1.
Conclusions: Eculizumab has shown promising results in our patients with refractory antiphospholipid syndrome. Longer follow-up of these patients will be needed in order to discern the effect on thrombosis. Controlled studies are needed to further assess the efficacy of eculizumab in this condition, as are mechanistic studies.

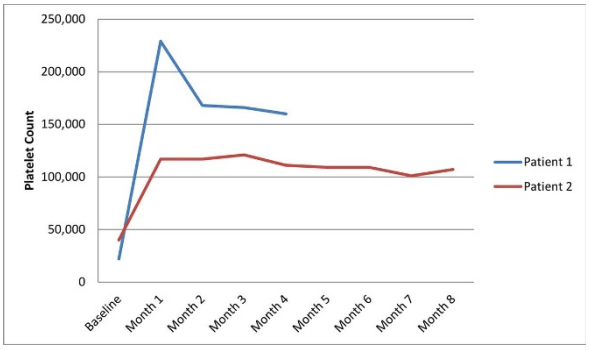

Figure 1(abstract A50) APS patients treated with eculizumab: platelet counts.

A51

A comprehensive approach to identify approved drugs and treatments for repositioning as therapies for systemic lupus erythematosus

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Background: Development of new systemic lupus erythematosus (SLE) treatments has been slow. To accelerate the pace, an evidence-based approach was developed to find new lupus therapies amongst 6,800 compounds FDA approved for human use.
Methods: The Lupus Treatment List (LRxL) was constructed with intense input from the entire lupus community, including patients, and was used to prioritize therapies to be tested in small focused, biomarker-rich clinical trials (SLE Treatment Acceleration Trials (STAT)). All drugs widely used for lupus or known to be in development for lupus by Pharma/Biotech were excluded. Details of the project can be viewed online [1]. A novel evidence-based composite scoring system was developed to rank the identified drugs/therapies numerically by scientific rationale, experience in lupus mice/human cells, previous clinical experience in autoimmunity, drug properties and adverse event profile.
Results: Of the 157 therapies initially screened, more than 25 have an appropriate set of characteristics to consider for testing in clinical trials in lupus, including drugs targeting cellular metabolism, kinases, the immune

system, HDACs, complement as well as cellular therapies and nondrug interventions.

Conclusions: This approach has not only identified unique candidates that could be useful in SLE and possibly other autoimmune/inflammatory conditions, but has also yielded a rigorous evidence-based process by which therapies can be usefully rated for possible clinical application to treat these conditions, thereby mitigating risk in drug development.

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A52

Cluster analysis of longitudinal treatment patterns in patients newly diagnosed with systemic lupus erythematosus in the United States

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Background: Treatments for systemic lupus erythematosus (SLE) include corticosteroids (CS), antimalarials, nonsteroidal anti-inflammatory drugs, cytotoxic agents, and immunosuppressive/immunomodulatory agents. We examined treatment patterns in newly diagnosed SLE patients from a multipayer US claims database.

Methods: This study (GSK HO-13-13054) retrospectively followed incident SLE patients' treatment for 4 years in the MarketScan commercial claims database. The earliest medical claim date with SLE diagnosis (ICD-9 code 710.0x; 1 January 2002 to 31 March 2008) was the index date. Patients were ≥18 years at index, had continuous medical and pharmacy benefits for 12 months pre index without SLE diagnosis and 48 months post index, with ≥1 SLE-related inpatient claim or ≥2 office or emergency room visits with SLE diagnosis ≥30 days apart within 12 months post index. A specialist must have made ≥1 SLE diagnosis at index or within 12 months post index. Results were stratified by provider type (primary care physician (PCP)/ specialist). A disjoint k-means cluster analysis identified treatment pathways using annual prescription numbers for CS, hydroxychloroquine (HCQ), mycophenolate mofetil, azathioprine, and methotrexate as input variables.

Results: The study identified 2,086 newly diagnosed SLE patients (mean age: 47.2 years; female: 91%). In the 4 years post index, 1,031 (49.4%) patients were not actively treated (<0.05 prescriptions/year). Of the 219 (10.5%) patients who primarily received CS, 42 had persistently high numbers of prescriptions (~1/month), and 177 received 4.9 (mean) prescriptions in Year 1, decreasing in Years 2 to 4. Three subgroups emerged within the 606 (29.1%) patients who primarily received HCQ: persistent high number of prescriptions (~1/month), persistent moderate number of prescriptions (3.2 to 4.1/year), and poor adherence (Year 1, 8.7 prescriptions; Years 2 to 4, decreasing prescriptions). Both CS and HCQ were received by 138 (6.6%) patients; 56 had high numbers of prescriptions (Years 1 to 4); 82 showed progressively decreasing prescriptions. Fifty-four (2.6%) and 38 (1.8%) patients had moderate numbers of prescriptions for methotrexate (5.4 to 8.4/year) and azathioprine (5.7 to 7.5/year), respectively, with some CS and HCQ prescriptions. Treatment patterns differed in patients seen by specialists versus PCPs ($P < 0.0001$). Specialist-treated patients had a lower no-treatment rate than PCP-treated patients, and higher rates in active treatment clusters (Table 1).

Conclusions: Treatment patterns were observed among SLE patients using medical resources. In the 4 years post diagnosis: ~50% of patients were not actively treated; 50% received CS, HCQ, and immunosuppressants with differing combinations, intensities, and adherence levels. Specialists provided more intensive treatment than PCPs.

Competing interests: CM, HK, JP, and SN are employees of and hold stock in GlaxoSmithKline. DJW is a consultant for GlaxoSmithKline.

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A53

Effects of atacicept on disease activity in patients with moderate to severe systemic lupus erythematosus: APRIL-SLE randomized trial

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Background: Atacicept is a fusion protein that inhibits B-cell stimulating factors BLyS and APRIL, which are elevated in systemic lupus erythematosus (SLE). Atacicept 150 mg (A150) was associated with reduced BILAG A and B flares in the APRIL-SLE study. We examined efficacy of atacicept in preventing flares of SLE disease activity by the BILAG organ system and modified SELENA SLEDAI flare index and assessed corticosteroid use during a previously reported trial of atacicept versus placebo (PLC).

Methods: Subjects with active SLE were treated with corticosteroid taper for 12 weeks. Subjects reaching BILAG C or D at weeks 10 and 12 were randomized at baseline 1:1:1 to receive PLC, atacicept 75 mg (A75) or A150 twice weekly every 4 weeks then weekly for 48 weeks. All patients received standard of care. Analysis was performed in the modified intention-to-treat population. BILAG and SELENA SLEDAI flares and corticosteroid usage were assessed 4 weekly.

Table 1(abstract A52) Longitudinal treatment patterns according to primary treatment by specialist or PCP

Cluster	Interpretation	Treated primarily by specialists[a]		Treated primarily by PCPs[a]	
		n	%	*n*	%
1	Not actively treated throughout (<0.05 (mean) annual prescriptions)	216	26.2	815	64.6
2	CS only: high number of prescriptions (chronic use)	29	3.5	13	1.0
3	CS only: moderate number of prescriptions with slow reduction	85	10.3	92	7.3
4	HCQ only: high number of prescriptions (chronic use)	102	12.4	56	4.4
5	HCQ only: moderate number of prescriptions (chronic use)	136	16.5	134	10.6
6	HCQ only: poor adherence	111	13.5	67	5.3
7	CS plus HCQ: high number of prescriptions (chronic use)	32	3.9	24	1.9
8	CS plus HCQ: poor adherence	51	6.2	31	2.5
9	Methotrexate: moderate number of prescriptions plus some prescriptions for CS and HCQ	34	4.1	20	1.6
10	Azathioprine: moderate number of prescriptions plus some prescriptions for CS and HCQ	28	3.4	10	0.8
Total		824	100.0	1262	100.0

[a]Patients who visited a specialist (including a rheumatologist, dermatologist, nephrologist, ophthalmologist, or oncologist) in >50% of SLE-related office visits were defined as primarily seen by specialists. Patients who visited PCPs in >50% of SLE-related office visits were defined as primarily seen by PCPs. The difference in treatment patterns between the two groups was statistically significant ($P < 0.0001$).

Table 1(abstract A53) Corticosteroid exposure post-randomization, modified intention-to-treat population

	Placebo	Atacicept 75 mg	Atacicept 150 mg
	(*n* = 154)	**(*n* = 157)**	**(*n* = 144)**
Zero dose increases, *n* (%)	108 (70.1)	115 (73.2)	122 (85.3)
	(*n* = 154)	(*n* = 157)	(*n* = 143)
Corticosteroids ≥20 mg/day, *n* (%)	43 (27.9)	39 (24.8)	17 (11.9)
Odds ratio		0.860	0.346
P value		0.563	0.001

Results: The A150 arm was terminated early due to two fatal pulmonary infections. A lower proportion of subjects with >1 BILAG system A or B flare was observed in A150 and A75 versus PLC. Proportions of subjects with BILAG flare in each organ system were reduced in A150 versus PLC, except for vasculitis, which had similar proportions between groups. BILAG flares were most commonly observed in mucocutaneous and musculoskeletal systems. Proportions of subjects with severe SELENA SLEDAI flare during treatment in a *post-hoc* analysis were 19%, 11%, and 13% for PLC, A75, and A150, respectively. There was a dose-proportional decrease in the number of subjects who had at least one increase in steroid dose, and an increase of ≥20 mg/day (Table 1). Atacicept induced substantial reductions in Ig levels, which lessened during follow-up but did not fully return to baseline over 24 weeks. Atacicept treatment effect was observed in subjects with BLyS or APRIL levels ≥ median, but not < median. The difference was most pronounced in patients with baseline BLyS and APRIL ≥ median. Atacicept-treated patients with greatest absolute decrease in IgG and IgM experienced fewest new flares.
Conclusions: Reduction of the individual BILAG system and severe SELENA SLEDAI flares and corticosteroid use was associated with A150 treatment. Analysis of potential predictive biomarkers identified a subgroup of patients with higher BLyS and APRIL levels at baseline more likely to benefit from treatment. Further studies are required to clarify safety and efficacy of atacicept in SLE patients and associations between biomarkers and clinical response to atacicept.
Trial registration: EudraCT: 2007-003698-13, NCT00624338
Competing interests: DI, DW and CG are consultants for Merck Serono S.A. YL and SW are employees of EMD Serono Inc.
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